Triglycerides and Heart Disease, Still a Hypothesis?

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Abstract

The purpose of this article is to review the basic and clinical science relating plasma triglycerides and cardiovascular disease. Although many aspects of the basic physiology of triglyceride production, its plasma transport and tissue uptake have been known for several decades, the relationship of plasma triglyceride levels to vascular disease is uncertain. Are triglyceride rich lipoproteins, their influence on HDL and LDL, or the underlying diseases leading to defects in triglyceride metabolism the culprit? Animal models have failed to confirm that anything other than early fatty lesions can be produced by triglyceride-rich lipoproteins. Metabolic products of triglyceride metabolism can be toxic to arterial cells; however, these studies are primarily *in vitro*. Correlative studies of fasting and postprandial triglycerides and genetic diseases implicate VLDL and their remnants, and chylomicron remnants in atherosclerosis development; but the concomitant alterations in other lipoproteins and other risk factors obscure any conclusions about direct relationships between disease and triglycerides. Genes that regulate triglyceride levels also correlate with vascular disease. Human intervention trials, however, have lacked an appropriately defined population, and have produced outcomes without definitive conclusions. The time is more than ripe for new and creative approaches to understanding the relationship of triglycerides and heart disease.

Keywords

lipoproteins; lipase; atherosclerosis; hyperlipidemia; vascular disease

INTRODUCTION

Why has defining the relationship between circulating triglycerides and vascular disease been so evasive? Experimental biologists, epidemiologists, and clinical trialists have struggled with this issue. Guideline panels have skirted the issue with recommendations to calculate and treat non-HDL cholesterol. As we will discuss, some view triglycerides as merely the markers for other lipoprotein or non-lipoprotein abnormalities, which might be the real disease culprits. After all, the hallmark of atherosclerosis is cholesterol not triglyceride accumulation in the artery. At this time a number of panels are considering guidelines for evaluation and treatment of human hypertriglyceridemia. This review is not

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meant to duplicate these efforts. Rather its role is to illustrate controversy and thereby suggest areas in need of experimental and clinical investigation.

TRIGLYCERIDE UPTAKE AND TRANSPORT

Plasma triglycerides are primarily produced by the intestines and the liver. Dietary triglycerides enter the circulation within chylomicrons. Triglycerides assembled from *de novo* synthesized fatty acids and from lipids returning to the liver are secreted in VLDL.

Chylomicron production and catabolism

Most dietary fat is digested by pancreatic enzymes that hydrolyze ester bonds and release free fatty acids (FFAs). In a seemingly wasteful process but one that allows transcellular movement of lipids, the FFAs are absorbed in enterocytes and then reesterified. Chylomicron formation requires assembly of triglycerides, phospholipids and apoproteins including apolipoprotein (apo) B48, apoA-I, apoA-IV, apoE and apoCs, and microsomal triglyceride transport protein (MTTP). Chylomicrons flow from the lymphatics to the circulation where they exchange some of their surface apoproteins; apoA-IV dissociates and the particles are enriched with apoC-II, the activator of lipoprotein lipase (LpL).

Several factors regulate plasma triglyceride levels either by altering lipolysis or secretion. One is low HDL itself. Almost all human HDL deficiencies are associated with hypertriglyceridemia. This was recapitulated in the apoA-I knockout mice. Increased triglyceride in this animal was ascribed to a defect in lipolysis due to a deficiency of HDL apoC-II[1]. Another possible cause of increased triglyceride, greater production, was found in liver specific ABCAI knockout mice [2].

Regulation of remnant catabolism

Triglyceride within the chylomicrons is converted into FFAs, monoglycerides and glycerol producing a smaller, lipid depleted remnant particle. Most remnant particles are cleared from the circulation via hepatic LDL receptors. The lack of major hypertriglyceridemia in LDL receptor knockout mice shows the importance of backup processes. In this regard knockouts of syndecan 1 proteoglycan[3], LDL receptor related protein (LRP1)[4] and scavenger receptor-B1[5] lead to defective uptake of remnant lipoproteins and, in some cases, modest hypertriglyceridemia. In the setting of lipoprotein overproduction, deficiency of the VLDL receptor also leads to hypertriglyceridemia, probably due to a defect in LpL actions [6–8]

Hepatic synthesis of VLDL triglyceride

Hepatic production of triglycerides is coupled to that of apoB-100 to form VLDL. ApoB production is relatively stable such that changes in liver triglyceride production with carbohydrate feeding leads to large VLDL with unchanged apoB production[9]. Fatty acids block apoB degradation and might be one reason for greater VLDL production in poorly controlled diabetes. In addition, insulin has been reported to increase apoB degradation, and in insulin resistant states less apo B degradation could lead to increased production and secretion of VLDL[10]. Moreover, insulin stimulates SREBP1c leading to increased *de novo* FFA synthesis[11].

Regulation of plasma triglyceride lipolysis

LpL-mediated triglyceride lipolysis creates remnants and begins the conversion of VLDL to LDL. Although most triglyceride within lipoproteins is within the core, it is believed that there is always some TG that is exposed on the lipoprotein surface[12]. Associated apoproteins may assist with surface triglyceride exposure. Chylomicrons are more rapidly removed from

the bloodstream than VLDL. The larger size of the chylomicron means that each particle has more triglyceride, so lipoprotein LpL interaction occurs with a lower LpL to triglyceride ratio. Two other factors might increase chylomicron lipolysis *in vivo*. The lower density and greater size increase the chance of a particle colliding with the capillary wall[13]. Both *in vitro* and *in vivo* data are consistent with a saturation of LpL at triglyceride concentrations of approximately 0.5 μM, 500 mg/dl [14, 15]. VLDL triglyceride levels above this are thought to prevent efficient hydrolysis of chylomicrons.

LpL is primarily synthesized in muscle (cardiac and skeletal) and adipose. Loss of LpL in the mouse heart causes hypertriglyceridemia[16] and transgenic expression in the heart completely corrects the hypertriglyceridemia that occurs in LpL knockout mice[17]. LpL is regulated by physical activity. Loss of skeletal muscle LpL, which is akin to detraining or forced inactivity, causes a shift from fatty acid to glucose oxidation, leads to a redistribution of triglyceride to heart and liver, increases lipid concentrations in these tissues, and leads to insulin resistance[18]. As opposed to the relatively minor changes in plasma triglycerides that accompany complete loss of receptors thought to mediate uptake of remnants into the liver, factors that reduce LpL actions produce dramatic hypertriglyceridemia. Several new proteins that affect lipolysis and that are involved in human disorders of chylomicron metabolism have been described recently and were reviewed in detail by Olivecrona et al.[19]. Angiopoietin like proteins 3 and 4 are tissue inhibitors of LpL actions and molecular defects are associated with lower triglyceride levels. ApoA-5 reduces plasma triglyceride but its mode of action is still uncertain. Glycosylphostidylinositol HDL binding protein (GPIHBP) appears to assist with LpL attachment to its physiological site of action on the luminal surface of endothelial[20].

Hypertriglyceridemia and LDL and HDL metabolism

Hypertriglyceridemia is associated with reduced HDL and small dense LDL (sdLDL) in humans. Experimental studies have shown how this occurs. Decades ago Havel et al. demonstrated that lipolysis releases apoCs that transfer to HDL and return to chylomicrons after feeding [21]. This transfer of apoproteins is accompanied by movement of lipids. In part for that reason, LpL inhibition leads to rapid and dramatic reductions in circulating HDL [22]. In the presence of cholesteryl ester transfer protein (CETP), which is not found in rodents, HDL reduction is due to both exchange of cholesteryl ester for triglyceride in triglyceride-rich lipoproteins and more rapid catabolism of the smaller triglyceride-enriched HDL [23, 24].

Why is hypertriglyceridemia associated with sdLDL? CETP will also mediate exchange of LDL cholesteryl esters for triglyceride. Triglyceride-enriched LDL are a substrate for LpL and hepatic lipase and may be the precursor to sdLDL[25]. Recently a kinetic study in humans suggested that large apoC-III-rich VLDL were preferentially converted to sdLDL[26].

EXPERIMENTAL EVIDENCE FOR THE ATHEROGENICITY OF TRIGLYCERIDE-RICH LIPOPROTEINS

Two pathways have been hypothesized to connect levels of circulating triglycerides with atherosclerosis. Zilversmit proposed that during the postprandial period chylomicrons were converted to remnants that could then penetrate the arterial wall and deposit cholesterol[27] (Figure 1 left). This process, he conjectured, correlated with the greater LpL activity in the artery associated with macrophage infiltration[28]. Evidence that chylomicron remnants are atherogenic is abundant. Remnant lipoproteins have been identified in the arteries of humans [29]. And unlike LDL, remnant lipoproteins can convert macrophages into foam cells[30]. Remnants are the causative factors in many accepted atherosclerosis models including the apoE knockout mouse and cholesterol-fed rabbits and monkeys. In the clinical

context, a major issue is quantification of remnants. In humans, chylomicron remnants contain apoB48 but measurements of this apoprotein have not been used in large clinical trials. In kinetic studies, retinyl ester has been used as a tracker that is contained in both chylomicrons and remnants; so triglyceride poor retinyl ester particles or apoB48 particles with a higher density than chylomicrons are operationally considered remnants.

Are non-remnant triglyceride-rich lipoproteins atherogenic? Atherosclerosis is a disease whose pathological fingerprint is cholesterol and not triglyceride accumulation within the artery. Thus, one must ask if nascent triglyceride-rich lipoproteins can deliver cholesterol to the vascular wall exclusive of their hydrolysis to remnants. The classic experiments by Duff et al.[31] showed that diabetes increased concentrations of large triglyceride-rich lipoproteins and reduced the number of remnants in the circulation of cholesterol-fed rabbits. This change in lipoprotein profile resulted in less atherosclerosis, i.e. diabetes was protective in this model. Several decades later the reason for this observation was uncovered when it was shown that the very large triglyceride-rich lipoproteins, perhaps equivalent to nascent chylomicrons, circulating in the diabetic rabbits were unable to enter the artery[32]. These studies contrast, but do not contradict, the demonstration by Rutledge et al. that VLDL can deposit in the wall of the perfused artery, especially in the presence of LpL[33]. Nor do they contradict the data showing that VLDL cholesterol levels correlate with atherosclerosis formation in LDL receptor knockout mice[34]. But it leaves unanswered whether VLDL size lipoproteins are a source of atherogenic cholesterol.

Studies of humans with genetic defects in LpL activity suggest that nascent lipoproteins are relatively, but not absolutely non-atherogenic. Until recently, a generally accepted view was that patients with severe hypertriglyceridemia were resistant to atherosclerosis[35]. A similar argument was made to account for the variation in coronary artery disease (CAD) risk in patients with genetic familial hypertriglyceridemias. Patients with familial hypertriglyceridemia (FHTG) appear to develop less CAD than those with familial combined hyperlipidemia (FCHL), perhaps due to their relatively cholesterol-poor VLDL[36]. However, the demonstration that LpL deficient patients are not entirely immune to vascular disease[37] has led to some uncertainty as to CAD risk with genetic hypertriglyceridemia syndromes.

Animal models support the hypothesis that larger triglyceride-rich lipoproteins are not totally harmless but are less atherogenic than smaller lipoproteins. Hypertriglyceridemic mice with deficiencies of LpL[38] or GPIHBP[39] develop small lesions, but at relatively advanced age. Thus, it appears that large triglyceride-rich lipoproteins can be atherogenic and deposit cholesterol in the artery, but they are much less atherogenic than smaller lipoproteins.

Atherogenicity of lipolysis products

Perhaps the major toxicity of triglyceride-rich lipoproteins is not from intact particles but from their lipolysis along the artery wall. Lipolysis of triglyceride-rich lipoproteins produces FFAs and lysolecithin (Figure 1 right). Recently, more complex lipid analysis has shown that lipolysis of VLDL leads to release of a number of additional potentially toxic oxidized fatty acids[40]. *In vitro* studies have implicated these lipids (and in some experiments triglyceride lipolysis) in inflammation [41], macrophage cytotoxicity [42], expression of adhesion molecules [43, 44], and promotion of coagulation[45, 46]. VLDL lipolysis, but not VLDL alone promotes an inflammatory response in cultured macrophages[47]. Extreme levels of lipolysis products created in the circulation by infusion of lipid emulsions in the presence of heparin activate toll-like receptors and downstream inflammatory pathways[48], whereas removal of FFA by their esterification to triglyceride [49, 50] reduces cellular inflammation. It

should be noted that *in vitro* studies have also implicated lipolysis products as anti-inflammatory molecules due to their activation of PPARs [51, 52].

Gain and loss of lipolysis has been studied in isolated arteries and using mice with genetic modifications of LpL. VLDL and LpL together allowed more LDL to enter the wall of an isolated perfused artery due to disruption in endothelial barrier function[53]. Loss of macrophage LpL in genetically modulated mice reduced plaques[37, 54, 55]. Similarly mice with heterozygous LpL deficiency had less atherosclerosis despite hypertriglyceridemia[56]. Although endothelial cells do not express LpL, an endothelial cell-expressing LpL transgene does create active enzyme[57]. Mice expressing endothelial cell LpL have defective vascular relaxation, however, this was only found in the presence of TNF. Smooth muscle LpL expression also leads to defective arterial relaxation[58]. Effects of these two LpL transgenes on atherosclerosis are under study. The many effects of LpL including its ability to alter macrophage inflammatory function and to anchor lipoproteins to matrix proteoglycans will complicate the interpretation of these studies[13], which are unlikely to provide more than correlative information relating lipolysis and vascular disease.

RELATIONSHIP OF TRIGLYCERIDES TO CLINCIAL CARDIOVASCULAR DISEASE (CAD)

Hypertriglyceridemia is perhaps the most difficult lipid disorder to evaluate and treat. Why is this? First, genetic disorders are quite common but most genes relevant to this common metabolic disorder have yet to be clearly identified. Second, hypertriglyceridemia associates with a number of acquired disorders, e.g. insulin resistant states. This raises an important issue as to whether the association of hypertriglyceridemia with CAD or other forms of atherosclerosis is a direct effect of the triglyceride-rich lipoproteins themselves or the company they keep. In addition, as reviewed elsewhere[59], triglyceride levels can fluctuate widely with diet and exercise.

Problems also exist in defining hypertriglyceridemia. Fasting levels are highly variable and non-fasting levels even more so, population data are skewed, and relationships between fasting or non-fasting triglycerides and CAD often do not relate to the extent of their elevation. When using a triglyceride value of <150 mg/dl to define normal, as is done in existing guidelines, the prevalence of hypertriglyceridemia in the US is 27.5% for subjects with a BMI of < 25 kg/m^2, 31% for those with a BMI between 25 and 30 kg/m^2, and 37% for those with a BMI > 30 kg/m[60]. And, with the obesity epidemic still expanding, this prevalence will certainly increase.

Triglycerides and other metabolic derangements

The metabolic syndrome is the best example illustrating the company that elevated plasma triglycerides keep[61]. The metabolic syndrome is a common metabolic disorder strongly related to central obesity. The pathophysiology seems to be largely attributable to insulin resistance and excessive flux of FFA. An inflammatory state likely contributes to the syndrome and an associated prothrombotic state contributes to CAD risk. The controversy about the definition of the metabolic syndrome was resolved and there is now a single global definition[62]. Criteria include increased waist circumference (population specific), increased triglyceride (>150,mg/dl), reduced HDL-cholesterol (<40 in man and <50 in women), hypertension (>130 systolic or 85 diastolic), and fasting glucose (>100 mg/dL). Because the metabolic syndrome relates to insulin resistance and captures a broad range of risk factors that relate to CAD, the independent relationship of triglyceride elevation per se to CAD is reduced. Similarly the other lipoprotein abnormalities that accompany metabolic syndrome, low HDL and sdLDL, might also be markers of the real process that increases CAD risk.

Clinical correlative studies of triglycerides and CAD

One of the earliest reports linking triglycerides to CAD was by Margaret Albrink[63]. In a small cross-sectional study, hypertriglyceridemia appeared to be more important than hypercholesterolemia in its association with CAD in men. Other data such as that from Framingham suggested that high plasma triglyceride levels were an even greater CAD risk factor for women[64]. This observation has been replicated in other studies[65, 66]. Within the setting of the metabolic syndrome, type 2 diabetes, and familial combined hyperlipidemia, a recent review has listed 11 published reports of the independence of plasma triglycerides as a risk factor for CAD, but also acknowledges the inconsistency of this relationship[67]. Thus, are plasma triglycerides a biomarker rather than an independent risk factor of CAD risk?

More recently non-fasting triglycerides have been implicated as equally predictive of CAD risk as fasting hypertriglyceridemia[68, 69]. In addition, non-fasting triglycerides were associated with stroke risk[70]. However, in general when levels of fasting triglycerides are elevated so are the postprandial triglyceride levels[71, 72]. In addition, non-fasting hypertriglyceridemia predicts a higher level of remnant cholesterol, another risk factor for CAD. The relative risk of either a 1.0 mM (90 mg/dl) elevation in fasting triglycerides or levels above 200 mg/dl is ~1.7[73–75]. However, when adjusting for levels of HDL cholesterol, the relative risk became minimally significant in men (1.14) and reduced in women (1.37)[74]. In general, this relatively higher independent risk in women is reproducible and without obvious explanation. Moreover, a more recent analysis by the Emerging Risk Factors Collaborators in over 300,000 people without CAD demonstrated a risk of 2.6 in the bottom tertile vs. 6.2 in the top tertile[76]. However, after adjustment for HDL cholesterol and other risk factors, this risk disappeared. Thus, these data suggest that plasma triglycerides are a biomarker rather than an independent CAD risk factor. In contrast, non-fasting triglycerides were associated with stroke risk in both men and women.

GENETIC INSIGHTS

Do genetic studies support a relationship between triglycerides and CAD? Recent genome-wide association studies (GWAS) have provided new insights into the regulation of plasma triglycerides with the identification of novel loci harboring genes that were subsequently identified to have a previously unknown function in triglyceride metabolism. For example, a region on chromosome 8 downstream of *TRIB1* (encoding tribbles homolog 1) was found to strongly associate with both plasma triglycerides and CAD risk. Further studies in mice demonstrated reciprocal effects of *Trib1* overexpression or knockdown on hepatic triglyceride synthesis and VLDL secretion [77]. GWAS have also lent plausibility to the hypothesis that triglycerides are causally related to CAD risk. The main rationale underlying the concept of "Mendelian randomization" is that if a given trait (e.g. elevated triglycerides) is causally related to an outcome (e.g. CAD), the genetic variants associated with the trait should have a similar relation to the outcome. Although the concept is simple, a number of conditions must be met including lack of pleiotrophic effects for a given genetic variant and lack of statistical interactions with other genetic or environmental factors. These criteria do not consistently apply to genetic variants affecting triglyceride metabolism[78].

Each step in hepatic and intestinal triglyceride synthesis, VLDL assembly and secretion, and intravascular lipolysis is regulated by multiple gene products. Coding and regulatory variants in a number of genes associate with alterations in HDL- and/or LDL-cholesterol as well as triglycerides. Importantly, triglyceride metabolism is highly sensitive to clinical and environmental conditions including obesity, physical activity, diet, hormonal states, circulating glucose levels and pro-inflammatory cytokines. These interact with genetic factors to regulate triglyceride metabolism. Of note, several triglyceride raising alleles exert greater effects in obese sedentary versus lean physically active individuals. Significant gene/

gene interactions are also evident[79, 80]. For example, the effects of the common *APOA5* 1132T>C variant on plasma triglycerides is enhanced in carriers of the *APOE*4 allele.

Furthermore, pleiotrophy is well documented at several genetic loci. For example, a common polymorphism (rs780094) -30G>A in *GCKR*, the gene encoding the glucokinase regulatory protein, is associated with both elevated fasting triglycerides and lower fasting glucose and reduced risk for diabetes[81]. No association of rs780094 with CAD has been documented, which may be explained by the opposing effects on CAD risk factors. In contrast, the gene encoding insulin receptor substrate 1, *IRS1*, is associated with higher plasma triglycerides and with CAD risk. Because the risk alleles also confer a greater propensity for insulin resistance and type 2 diabetes, the effects on CAD risk are likely due to multiple metabolic effects [82].

Associations of genes for triglyceride metabolism and CAD

Despite these confounders, genetic studies are generally consistent with a role for triglyceride-mediated pathways in CAD. The Global Lipids Consortium recently reported on 95 loci associated with plasma lipid traits in over 100,000 individuals of European ancestry[83]. In a further analysis including 24,607 individuals with CAD and 66,197 controls, association of lipid SNPs with CAD was tested (Table 1). Most loci associated with LDL-cholesterol altered CAD risk in the expected direction. A smaller number of loci primarily associated with triglycerides also increased CAD risk. These included single nucleotide polymorphisms in genes encoding LpL, tribbles 1 (*TRIB1*), N-acetyltransferase 2 (*NAT2*) and the *ZNF259/APOA5/APOA4/APOC3/APOA1* gene cluster. Certain of these genes/gene clusters are associated with multiple lipid traits. The gene product of *TRIB*1 regulates hepatic triglyceride synthesis and, although most strongly associated with triglycerides, also associates with HDL- and LDL-cholesterol levels[77]. The 11q23 locus encompassing *ZNF259, APOA5, APOA4, APOC3* and *APOA1* is most strongly linked to triglycerides but has multiple effects on other lipoproteins. Studies in genetic isolates also support a role for regulators of the triglyceride lipolytic pathway in atherosclerosis. ApoC-III inhibits triglyceride lipolysis and a null mutation in human *APOC3* (R19X) with a carrier frequency of 5% in the Lancaster Amish is associated with lower plasma triglycerides and cardioprotection[84]. Moreover, increases in apoC-III-containing lipoproteins may confer risk beyond that of other risk factors [85].

The Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration recently reported on the association of the -1131T>C (rs662799) promoter polymorphism of the apoA5 (*APOA5*) gene with triglycerides and CAD in 20,842 CAD patients and 35,206 controls[86]. The -1131T>C polymorphism is in almost complete linkage disequilibrium with two other *APOA5* polymorphisms, -3A>G (rs651821) and +1891T>C (rs2266788) and, by decreasing *APOA5* gene expression, the risk haplotype would be expected to lead to impaired lipolysis of TG-rich lipoproteins [58, 87]. In this large meta analysis, the minor allele of rs662799 (minor allele frequency, 0.08) was associated with an allele specific increase in triglycerides of 16% (CI 12.9–18.7) and an odds ratio for CAD of 1.18 (CI 1.11–1.26; $p=2.6 \times 10^{-7}$), consistent with the reported hazard ratio of 1.10 (CI 1.08–1.12) for a 16% increase in triglycerides in prospective population studies. Although this locus primarily associates with plasma triglycerides, a smaller but significant effect on HDL-cholesterol (−3.5%) may have also contributed to the observed CAD risk.

Overall genetic studies support the hypothesis that impairment of triglyceride lipolytic pathways is associated with increased CAD risk although the extent to which risk is mediated by increased triglyceride-rich lipoproteins, altered LDL size and composition, or decreased HDL-cholesterol is not entirely clear. Other loci identified to associate with triglycerides in multiple genome-wide association studies are less clearly associated with

increased CAD risk[58, 88] (Table 1). These include *MLXIPL (CHREBP)* encoding the carbohydrate response element binding protein and *FADS2,3* encoding the fatty acid desaturases, which play important roles in hepatic triglyceride synthesis. This may lead to the conclusion that regulation of hepatic triglyceride synthesis is less relevant for atherosclerosis than regulation of lipolysis. However, the *TRIB1* gene product is another regulator of hepatic triglyceride synthesis and, unlike *MLXIPL* and *FADS2,3*, is clearly related to CAD risk. Further functional analysis of these triglyceride associated loci may provide further mechanistic insight into triglyceride metabolism and atherosclerosis susceptibility.

As reported by Hegele et al.[89], multiple SNPs associated with triglycerides in genome wide association and candidate gene studies are significantly associated with hypertriglyceridemia phenotypes including FCHL and FHTG, indicating that FCHL and FHTG are polygenic traits with considerable overlap. Rare variants[90] and common SNPs[91] at multiple triglyceride-associated loci contribute cumulatively to the severity of hypertriglyceridemia. Notably, both FCHL and FHTG are strongly associated with CAD risk particularly when other features of the metabolic syndrome are present [92].

CLINICAL TRIALS OF TRIGLYCERIDE REDUCING THERAPIES

Do human clinical trials support triglyceride reduction as a means to reduce CAD risk? Unfortunately such trials have suffered from experimental design and are few in number. The overall findings are hypothesis-generating at best. Because of the complex interactions of plasma lipoproteins and the lack of drugs to specifically lower triglyceride levels, only limited pathophysiologic insights have been unveiled by clinical trials.

The most selective of the triglyceride-reducing drugs are the fibrates. It s unfortunate that the trials to examine if fibrates reduce CAD events have been inadequate to address the hypothesis. At best, we are left with post hoc analysis to establish the optimal trial to follow, i.e. in hypertriglyceridemic patients in whom LDL lowering therapy with a statin has already been instituted. Four major fibrate trials to test the hypothesis that the reduction in fasting (and presumably postprandial) plasma triglycerides reduces the incidence of acute myocardial infarction (MI) or death from cardiovascular causes have been completed in patients with CAD or high risk (Table 2). This subgroup analysis suggests that hypertriglyceridemic patients with low HDL do benefit from fibrates.

Should fibrates remain the drug class of choice to lower triglycerides in patients with hypertriglyceridemia? Based on the data we have, the answer appears to be yes. As stated in a very recent meta-analysis of the effects of fibrates on CAD outcomes[93], fibrates can reduce the risk of major cardiovascular events and might have a role in individuals at high risk of cardiovascular events and in those with combined dyslipidemia. This however remains to be proven.

Higher doses of omega-3 ethyl esters (EEC) (2.0–4.5 g of EPA + DHA) lower plasma triglycerides with very little effect on plasma levels of LDL or HDL cholesterol; high doses of omega-3 EEC lower triglycerides by ~30–35% by a number of mechanisms[94]. The studies of effects of omega-3 fatty acids on cardiovascular disease are conflicting but their actions might be via processes exclusive of triglyceride reduction. In the GISSI-Prevenzione study, 11,324 CHD patients with a recent MI appeared to benefit from omega-3 EEC 1000 mg/day although the amount of triglyceride lowering was small and was not related to the CVD benefit[95]. However, a recently published trial performed in northern Europe failed to show a beneficial effect of a similar treatment[96]. Two other omega-3 EEC studies are worth noting; the Diet and Reinfarction Trial (DART)[97], and The Japan EPA Lipid Intervention Study (JELIS)[98]. In DART, the omega-3 EEC group had an initial reduction in re-infarction

by 32% and a 29% reduction in all cause mortality, but the 21,147 person year follow-up failed to demonstrate a long-term survival benefit of higher levels of fish consumption; the fish oil consumption group had a significant increase in sudden cardiac death (P=0.018). JELIS was a large trial in 18,645 patients with hyperlipidemia of whom more than 3500 had a history of a CAD event. Subjects were randomly assigned to either a statin alone or a combination of statin and 1.8 g of EPA daily. After 5 years, the combination treatment was associated with a significant 19% reduction of the primary composite endpoint comprising death, revascularization, MI and unstable angina compared to the statin alone group. The greatest relative risk reduction of 53% was experienced in patients in the primary prevention arm who had hypertriglyceridemia (mean, 272 mg/dl) and decreased HDL-cholesterol levels despite only a 5% difference in the amount of triglyceride lowering in the statin-EPA vs. the statin alone group. It is important to point out that subjects in both GISSI-Prevenzione and JELIS had levels of LDL cholesterol far above current goals. Thus, although omega-3 fatty acids appear to reduce CAD events in some high risk populations, as for other triglyceride lowering therapies the benefit appears unrelated to the triglyceride lowering effect.

Niacin (nicotinic acid) is a lipid altering vitamin used in high doses to favorably modify triglycerides; the molecular/cellular effects of niacin remain uncertain[99]. Presently the completed niacin trials have been insufficient in size and design to determine whether or not niacin has independent benefits on CAD, and whether or not the reduction in risk for CAD is secondary to triglyceride lowering. Large randomized clinical trials are in progress. Smaller studies of CAD in consort with other lipid reducing agents [100] or of carotid plaques in statin-treated subjects[101] show beneficial effects of niacin. However, because niacin also reduces LDL and raises HDL - and may lower lipoprotein (a) - benefit in clinical studies cannot be ascribed solely to reduction in triglyceride.

Moderate to high doses of the more potent statins lower triglycerides. Statins have been reported to decrease hepatic secretion of apoB containing lipoproteins[102]. They might also increase VLDL and chylomicron clearance secondary to upregulation of the LDL receptor. Observational evidence from the GREACE Study suggests that that the decrease in triglycerides in statin (mainly atorvastatin)-treated CAD patients correlated with CAD event reduction; this effect was pronounced in patients with the metabolic syndrome[103]. In contrast, data from the Treating to New Targets study showed that benefit due to intensive lipid-lowering therapy with atorvastatin was not related to the modest 10% fall in fasting plasma triglycerides[104].

CONCLUSIONS AND AREAS IN NEED OF SCIENTIFIC STUDY

Although hypertriglyceridemia is a common biochemical abnormality in humans, except for pancreatitis risk, its relationship to human disease is far from certain. Is hypertriglyceridemia merely a marker of other metabolic abnormalities, or does it initiate or accelerate progression of vascular disease? Does this only occur in specific genetic or environmental settings? Despite the plethora of data showing atherogenic-like effects of lipids or lipolysis products on cultured cells, animal models to allow the study of the effects of hypertriglyceridemia on arteries *in vivo* are needed. Perhaps it s not the triglycerides themselves, but VLDL particle number or changes in HDL or LDL that are most important for vascular biology. Studies further exploring the link of genetic variants to hypertriglyceridemia and CAD are in progress. Importantly, the development of specific drugs to lower triglycerides would allow one to directly test in humans whether triglyceride reduction reduces CAD events. The correct trial in patients with hypertriglyceridemia needs to be performed. At this point, such drugs and clinical trials are but a dream. Thus, the hypothesis that triglycerides are an independent risk for human vascular disease will be around to challenge the next generation of basic and clinical scientists.

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Atherogenicity of Triglyceride-Rich Lipoproteins (TGRL)
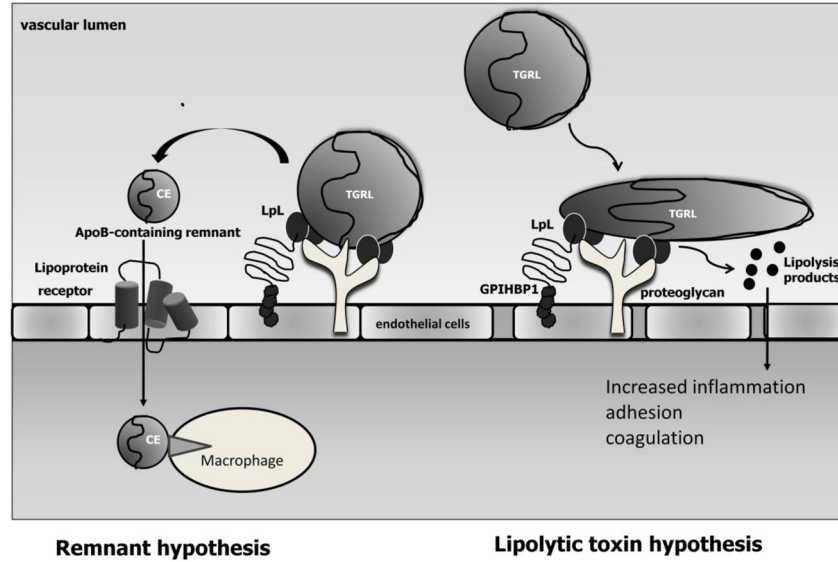
Figure 1. Atherogenicity of triglyceride-rich lipoproteins
Two hypotheses for pathways by which triglyceride-rich lipoproteins (TGRL) might increase atherosclerosis are illustrated. Left panel shows the remnant infiltration hypothesis. Conversion of TGRLs to remnants produces particles that then enter the arterial wall, carrying both triglyceride and cholesterol. Arterial LpL may be important to increase the local concentration of these particles. Remnants can be internalized by macrophages and convert these cells into foam cells. Right panel illustrates the toxic lipolysis product hypothesis. During lipolysis of TGRLs a number of inflammatory lipids are released that alter endothelial biology. These lipids - including fatty acids lysolecithin and oxidized lipids - increase expression of adhesion molecules and cytokines, and promote coagulation.

Table 1

Association of Triglyceride SNPs Identified in Genome wide Association Studies with CAD

Gene	Chr	lead SNP	Alleles	MAF	effect size (mg/dl)	CAD Association
ANGPTL3	1	rs2131925	T/G	0.32	−4.94	
APOB	2	rs1042034	T/C	0.22	−5.99	
GCKR	2	rs1260326	C/T	0.41	+8.76	
COBLL1	2	rs10195252	T/C	0.40	−2.01	
MSL2L1	3	rs645040	T/G	0.22	−2.22	
KLHL8	4	rs442177	T/G	0.41	−2.25	
MAP3K1	5	rs9686661	C/T	0.20	+2.57	
HLA	6	rs2247056	C/T	0.25	−2.99	
TYW1B	7	rs13238203	C/T	0.04	−7.91	
MLXIPL	7	rs17145738	C/T	0.12	−9.32	
PINX1	8	rs11776767	G/C	0.37	+2.01	
NAT2	8	rs1495741	A/G	0.22	+2.85	+
LPL	8	rs12678919	A/G	0.12	−13.64	+
TRIB1	8	rs2954029	A/T	0.47	−5.64	+
JMJD1C	10	rs10761731	A/T	0.43	−2.38	
CYP26A1	10	rs2068888	G/A	0.46	−2.28	
FADS1-2-3	11	rs174546	C/T	0.34	+3.82	
APOA5	11	rs964184	C/G	0.13	+16.95	+
LRP1	12	rs11613352	C/T	0.23	−2.70	
CAPN3	15	rs2412710	G/A	0.02	+7.00	
FRMD5	15	rs2929282	A/T	0.05	+5.13	
CTF1	16	rs11649653	C/G	0.40	−2.13	
CILP2	19	rs10401969	T/C	0.07	−4.74	+
APOE	19	rs439401	C/T	0.36	−5.50	+
PLA2G6	22	rs5756931	T/C	0.40	−1.54	

MAF (minor allele frequency) (reference 80 Teslovich et al.)

TABLE 2

Fibric acid intervention trials

Study	Drug	n	TG (Criteria)	TG ↓	Primary Endpoint
VA-HIT (DM)	Gemfibrozil	2531 (550)	160 mg/dl (<300)	31%	24%
BIP (DM)	Bezafibrate	3090 (330)	145 mg/dl (<300)	21%	7%
FIELD (DM)	Fenofibrate	9795	156 mg/dl (90–450)	29%	11%
ACCORD-LIPID (DM)	Fenofibrate	2532	162 mg/dl (<400)	20%	8%