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Triglyceride-Rich Lipoproteins

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Introduction

- What are the types and key features of triglyceride-rich lipoproteins (TGRLs)?
- What are the endogenous and exogenous metabolic pathways of TGRLs?
- What is the role of polymorphisms in metabolic abnormalities of triglycerides?
- What role do TGRLs play in atherosclerotic cardiovascular disease (ASCVD)?

Triglyceride-Rich Lipoproteins (TGRL)

TGRL	Definition
Chylomicrons	Large TGRL particles, produced by the small intestines, are involved in the transport of dietary TG and cholesterol to peripheral tissues and the liver. Apo B-48 is the core structural protein, with each particle containing 1 molecule. The amount of digested fat determines molecule size.
Chylomicron remnants	Smaller atherogenic particles, enriched in cholesterol, result from the removal of TG from chylomicrons by peripheral tissues.
Very low-density lipoproteins (VLDL)	TGRL particles produced by the liver with each particle containing 1 Apo B-100 molecule as the core structural protein. Particle size is dependent on TG quantity. VLDL particles are smaller than chylomicrons.
Intermediate-density lipoproteins (IDL; VLDL remnants)	The removal of TG from VLDL by muscle and adipose tissue results in the formation of IDL particles, which are enriched in cholesterol. These proatherogenic particles contain Apo C-III, Apo B-100 and Apo E.

Apo=apolipoprotein; TG=triglyceride; VLDL=very low-density lipoprotein.

Feingold KR, Grunfeld C. *NCBI Bookshelf*. South Dartmouth (MA): MDText.com, Inc.; 2000. <https://www.ncbi.nlm.nih.gov/books/NBK305896>.

TGRL Heterogeneity and Determinants of Plasma TG Levels

VLDLs of hepatic origin can be subdivided on the basis of their size and role in TG metabolism.

**VLDL1 are larger,
less dense particles
(Sf 60-400)**



**VLDL2 are
smaller particles
(Sf 20-60)**

- VLDL1 particles are the major determinant of plasma TG concentrations in normal and insulin-resistant individuals.
- Hepatic over-secretion, linked to increased liver fat and hyperglycemia, and/or impaired clearance of TGRL remnants from circulation, causes increased levels of VLDL1.

TG = triglyceride; TGRL = triglyceride-rich lipoproteins; VLDL = very low-density lipoprotein.

Dallinga-Thie G, et al. *Curr Cardiol Rep.* (2016) 18(67):1-9.

Triglyceride-Rich Lipoproteins and Genetics

- Over the past 15 years, human genetic studies have identified new proteins involved in TGRL metabolism, revealed insights into the genetic architecture of plasma TG, and clarified the contribution of TGRL to CVD.
- Postprandial TG metabolism abnormalities are also strongly associated with SNPs at common genetic loci, suggesting genetic mediation of interindividual variation in postprandial lipemia.
- These associations persist after accounting for effects on other lipid traits, including LDL-C, HDL-C, and lipoprotein concentrations.
- The Apo A5 locus has the strongest causal association between non-fasting TG and incident CVD.
- Genome-wide association studies reliably demonstrate that polymorphisms in or near the Apo A5 locus are associated with non-fasting TG levels.
- Associations between Apo A5 genetic variants and incident CHD were recently reported to be in direct relation to increases in elevated non-fasting TG and remnant cholesterol.

Apo = apolipoprotein; CHD = congenital heart defect; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SNP = single-nucleotide polymorphism; TG = triglyceride; VLDL = very low-density lipoprotein.

Rosenson R, et al. *JACC*. (2014) 64(23):2525-2540.

Role of TGRLs in ASCVD

- Increasing evidence suggests that remodeled chylomicrons and VLDL are atherogenic, primarily as a result of their progressive enrichment with cholesterol and TG depletion in the plasma compartment.
- Although LDL is considered the main atherogenic cholesterol-rich particle, other Apo B-containing lipoproteins (TGRL, their remnants, and Lp(a)) also contribute to intimal cholesterol deposition, particularly as they contain a similar number of cholesterol molecules per particle (~2000) as LDL.
- In dyslipidemic patients with cardiometabolic risk, increased FFA flux may represent a significant abnormality driving increased hepatic assembly and secretion of VLDL, IDL, and/or LDL particles.
- The retention of cholesterol-rich lipoproteins within the subendothelial matrix of the arterial wall is a key initiator of atherosclerosis.
- Experimental studies show that particle size is a key determinant of intimal cholesterol deposition contributing to atherothrombosis. While large chylomicrons and VLDL fail to penetrate the arterial wall, their smaller remnants not only penetrate the arterial intima but may be bound and retained by connective tissue matrix.

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease;
FFA = free fatty acids; IDL = intermediate-density lipoprotein;
LDL = low-density lipoprotein; Lp(a) = Lipoprotein(a); TG = triglyceride;
TGRL = triglyceride-rich lipoproteins; VLDL = very low-density lipoprotein.

Chapman et al. *European Heart Journal*. (2011) 32:1345–1361.

TGRL Role in ASCVD

- Accumulation of both chylomicron and VLDL remnants enriched in Apo E has been demonstrated and can be taken up directly by arterial macrophages with massive cholesterol loading and foam cell formation.¹
- Elevated levels of TGRL remnants have also been linked to CAD progression and the presence of echolucent carotid artery plaques.¹
- TGRL remnant cholesterol can contribute directly to plaque formation and progression.¹
- Several species of TGRLs appear to promote atherogenesis independently of LDL.²
 - Remnant species result from partial hydrolysis by LPL of TGRLs of hepatic and intestinal origin that have picked up cholesterol esters from HDL through CETP action.
 - Similar to oxidized LDL, these cholesterol-enriched, TG-poor species are subject to endothelial accumulation and uptake by macrophages to form foam cells.
 - Foam cells promote fatty streak formation, the precursor of atherosclerotic plaque.

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease;
CAD = coronary artery disease; CETP = cholesteryl ester transfer protein;
LDL = low-density lipoprotein; LPL = lipoprotein lipase; TG = triglyceride;
TGRL = triglyceride-rich lipoproteins; VLDL = very low-density lipoprotein.

1. Chapman et al. *European Heart Journal*. (2011) 32:1345-1361.
2. Talayero B, Sacks F. *Curr Cardiol Rep*. (2011) 13(6):544-552.
doi:10.1007/s11886-011-0220-3.

Summary and Conclusions

- Chylomicrons, produced by the small intestine, and VLDLs, produced by the liver, along with their associated remnants, are TG-rich lipoproteins that play a critical role in atherogenesis.
- Apolipoproteins associated with TGRLs impact LPL activity and serve as mediators in TGRL metabolism. TGRL metabolism consists of:
 - An endogenous pathway whereby VLDL and its associated remnants are produced by the liver
 - An exogenous pathway whereby chylomicrons and its associated remnants are produced by the small intestine.
- Research over the past 15 years have revealed new proteins and polymorphisms that play a role in TGRL contribution to ASCVD.
- Recent data support the hypothesis that VLDL-C or remnant cholesterol is even more atherogenic than LDL-C.

ASCVD = atherosclerotic cardiovascular disease; CHD = congenital heart defect; LDL = low-density lipoprotein; LPL = lipoprotein lipase; TGRL = triglyceride-rich lipoproteins; VLDL = very low-density lipoprotein.