Triglyceride-Rich Lipoproteins

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KEYWORDS

• Triglycerides • Triglyceride-rich lipoproteins • Cardiovascular risk • Triglyceride-lowering therapy • Lipoprotein lipase • Apolipoprotein CIII • Angiopoietin-like proteins

KEY POINTS

- A substantial residual cardiovascular risk remains after effective lowering of plasma low-density lipoprotein cholesterol.
- A causal relationship between plasma triglyceride (TG) levels and risk of cardiovascular disease has been indicated by Mendelian randomization studies and epidemiologic studies.
- TG metabolism is complex: genetic association studies have identified LPL, apoCIII, apoAV, ANGPTL3/4, LMF1, GPIHBP1, and TRIB1 as important regulators of TG levels.
- There are numerous emerging pharmacologic and biological therapies for elevated TG.

INTRODUCTION

Elevated levels of triglyceride-rich lipoproteins (TRLs), the main carriers of triglycerides (TG) in the blood, have been associated with an increased risk of cardiovascular disease (CVD) for decades. It has been debated whether increased plasma TG are causally linked to CVD. The difficulty in establishing causality between plasma TG levels and an increased risk of CVD is due to the postprandial variability of TG levels, which makes associations difficult, the confounding association with decreased high-density lipoprotein (HDL) levels, and the fact that subjects with extremely high TG levels do not typically develop CVD.[1] Recent genetic association and Mendelian randomization studies have identified many loci linked with TG, of which 7 are causally associated with CVD independently of plasma high-density lipoprotein cholesterol (HDL-C) or low-density lipoprotein cholesterol levels (LDL-C).[2] Because a substantial risk for CVD remains even after effective lowering of LDL-C, this and other studies relating to genetic deficiencies of apolipoproteinCIII (apoCIII) and angiopoietin-like proteins (ANGPTLs)[3,4] have sparked renewed interest in elevated TG levels as valid independent targets in the prevention of CVD. Here, the authors summarize their understanding of TG-rich lipoproteins and their relevance as candidate targets for therapeutic intervention.

TRIGLYCERIDE METABOLISM

Although classifications of severity vary between guidelines, plasma TG levels are generally considered elevated greater than 150 mg/dL (1.7 mmol/L). Severely elevated levels are greater than 885 mg/dL (10 mmol/L).[5] The standard measurement of plasma TG is performed under fasting conditions. However nonfasting levels have become accepted and are suggested to represent a more true reflection of average TG concentrations. Importantly, both elevated fasting and nonfasting concentrations of TG are associated with increased risk of CVD.[6]

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In the circulation, TG are carried within a variety of lipoproteins, transporting TG to and from tissues depending on demand. TG are most abundant in intestine-derived chylomicrons and in liver-derived very low-density lipoproteins (VLDL). Remnant lipoproteins such as intermediate-density lipoprotein (IDL) and chylomicron remnants, as well as HDL, also contain TG. It is important to note that the cholesterol content of TG-containing lipoproteins may link them causally to increased atherosclerotic plaque development.[7] Unlike VLDL and chylomicrons, remnant particles are small and have been demonstrated to enter the arterial wall.[8] It has been estimated that remnants contain 40 times more cholesterol compared with LDL and could therefore contribute substantially to cholesterol accumulation in the arterial wall.[9] Particle size may also explain why subjects with severe hypertriglyceridemia do not develop CVD because large chylomicrons do not enter the arterial wall.[9]

Postprandially, diet-derived fatty acids are used to synthesize TG, which are subsequently packed into chylomicrons containing apolipoproteinB48 by intestinal microsomal triglyceride transfer protein (MTTP). The chylomicrons are released from the intestine into the lymph before entering the blood, where hydrolysis of TG quickly converts these large chylomicrons into smaller chylomicron remnants, which are cleared by the liver.

In the liver, TG are assembled from fatty acids that are either synthesized locally or derived from the circulation. TG are packed into VLDL in a stepwise process lipidating apolipoproteinB100 (apoB) during translation in the rough endoplasmic reticulum (ER). Further addition of lipids by MTTP generates triglyceride-poor VLDL2. Subsequent fusion with TG-rich particles in the smooth ER leads to the formation of larger TG-rich VLDL1.[10] VLDL formation is highly dependent on the availability of both lipids and apoB, and a proportion of newly synthesized apoB is degraded intracellularly.[11] Although both VLDL1 and VLDL2 are secreted from the liver, it is VLDL1 that primarily contributes to plasma TG levels. Lipolysis on the capillary endothelium via lipoprotein lipase (LPL) converts VLDL into IDL, and further, lipolysis via hepatic triglyceride lipase (HTGL) on the luminal surface of endothelial cells in liver sinusoids generates LDL. LPL activity is promoted by apolipoproteinCII (apoCII) and apolipoproteinAV (apoAV) and inhibited by apolipoproteinCIII (apoCIII) and ANGPTLs.[9] As a consequence, genetic increases in apoCIII and loss of function (LOF) in apoAV increase TG levels and the risk of coronary disease, and decreased or LOF of apoCIII or ANGPTL3/4 decreases plasma TG and the risk of CVD.[3,4]

HDL acquires TG through the action of cholesteryl ester transfer protein, which mediates the exchange of cholesteryl esters and TG between HDL and apoB-containing lipoproteins. ApolipoproteinAIV (apoAIV) is added to chylomicrons during their formation in the intestine, whereas apoAV is added to VLDL during synthesis in the liver. In the circulation, exchange of apolipoproteins between TRLs and other lipoproteins occurs leading to an increase in apoCII, apoCIII, and apoE content and a decrease in apoAIV or apoAV.

Clearance of TRLs is mediated by LPL. Bound to heparin sulfate proteoglycans (HPSGs) on the surface of endothelial cells, LPL releases fatty acids for uptake by tissues, thereby generating triglyceride-containing remnants. During this process, lipids and proteins are transferred to HDL, explaining the tight link between TRLs and HDL levels. TRLs and remnants are taken up by the liver via interaction with HSPGs, the low-density lipoprotein receptor (LDLr), the low-density lipoprotein receptor related protein-1 (LRP1), and possibly the scavenger receptor type-1.[12] Small remnants bind the LDLr via apoE or apoB, while larger remnants are cleared via binding of apoE to HSPGs, LPL, HTGL, and other undefined receptors.[12] TG that are taken up in the liver are either resecreted or catabolized via β-oxidation. Although VLDL catabolism is much slower than that of chylomicrons, the clearance of chylomicrons and VLDL is understood to be mediated through the same pathways. Therefore, conditions leading to increased chylomicron levels will affect plasma VLDL levels and vice versa. Several factors that regulate LPL activity and TRL clearance are discussed later.

CAUSES OF HYPERTRIGLYCERIDEMIA

There are many factors that can contribute to elevated TG levels, which include genetic and nongenetic factors.[5,13] Severe hypertriglyceridemia can be caused by monogenic LOF mutations in *LPL*, *APOCII*, *APOAV*, lipase maturation factor-1 (*LMF1*), glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein-1 (*GPIHBP1*), and glycerol-3-phosphate dehydrogenase. Most of these are linked to inhibited clearance of TRLs. Monogenic LOF mutations are particularly rare. Polygenetic hypertriglyceridemia is more common, leads in general to moderate hypertriglyceridemia, and can be linked to the presence of multiple predisposing genetic variants. More than 40 common single-nucleotide polymorphisms (SNP) have been identified, many linked to pathways not previously known to affect plasma triglyceride levels. Each SNP has a small effect on TG levels explaining the wide