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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Genetics and Causality of Triglyceride-Rich Lipoproteins in Atherosclerotic Cardiovascular Disease

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ABSTRACT

Triglycerides represent 1 component of a heterogeneous pool of triglyceride-rich lipoproteins (TGRLs). The reliance on triglycerides or TGRLs as cardiovascular disease (CVD) risk biomarkers prompted investigations into therapies that lower plasma triglycerides as a means to reduce CVD events. Genetic studies identified TGRL components and pathways involved in their synthesis and metabolism. We advocate that only a subset of genetic mechanisms regulating TGRLs contribute to the risk of CVD events. This "omic" approach recently resulted in new targets for reducing CVD events. (J Am Coll Cardiol 2014;64:2525–40) © 2014 by the American College of Cardiology Foundation.

Triglyceride-rich lipoproteins (TGRLs) comprise a vast array of intestinally derived and hepatically secreted particles with distinct compositions and associations with risk for cardiovascular disease (CVD) or pancreatitis. Although the contribution of plasma/serum triglycerides (triacylglycerols [TG]) to increased risk of coronary and cerebrovascular ischemic events was established in multivariate models that adjust for major risk markers, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (1,2), elevated TGRLs alter low-density lipoprotein (LDL) and high-density lipoprotein (HDL) composition and function, which may result in unaccounted risk in observational studies and clinical trials of lipid-modifying therapies. Despite the association of circulating TGRL levels with atherosclerosis, whether abnormal TGRL metabolism and/or TGRL lipolytic products are causal remains uncertain.

The mechanisms underlying TGRLs and atherosclerotic CVD risk are incompletely understood. Mendelian randomization studies provide evidence for causal involvement of TG-mediated pathways in coronary heart disease (CHD); however, the contribution of TGRLs per se was not directly assessed (3). Furthermore, in clinical trials, TG-lowering therapies

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ABBREVIATIONS AND ACRONYMS

Apo = apolipoprotein

CHD = coronary heart disease

CVD = cardiovascular disease

DGAT = diacylglycerol acyltransferase

HDL = high-density lipoprotein

LDL = low-density lipoprotein

PPAR = peroxisome proliferator-activated receptor

TG = triacylglycerols

TGRLs = triglyceride-rich lipoproteins

VLDL = very low-density lipoprotein

not only alter TGRL concentration and composition, but also affect LDL, HDL, and inflammatory pathways.

This state-of-the-art review discusses the complexities of TGRL-associated atherosclerotic CVD risk and new directions in risk assessment and therapeutic responses to TG-lowering therapies from genetic studies. It is not intended to reiterate recent consensus statements on hypertriglyceridemia definitions, diagnosis, and management (4,5).

TGRL, HUMAN ATHEROSCLEROSIS, AND ATHEROSCLEROTIC CARDIOVASCULAR EVENTS

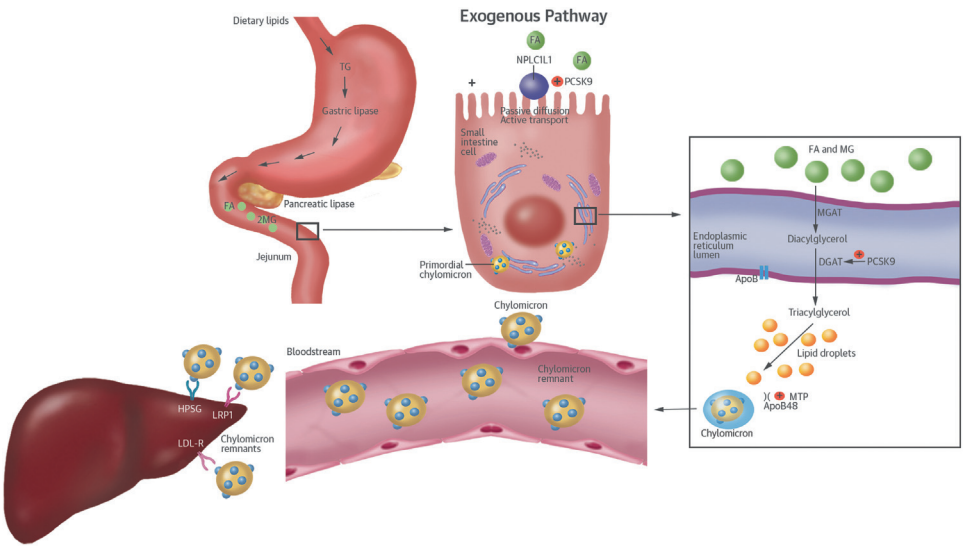
Chylomicron and very low-density lipoprotein (VLDL) remnants rapidly penetrate the arterial wall and contribute cholesterol to atherosclerotic lesions (6–8). VLDL composition is a critical CVD risk determinant. In retrospective and prospective population studies, TG-associated CHD risk was limited to apolipoprotein (Apo) C3-containing VLDL particles and their metabolic remnants, small LDL particles (9–11). VLDL proteome analysis expanded the complexities of VLDL through identification of 33 functional pathways, including 4 related to lipid transport and lipoprotein metabolism, and 8 associated with coagulation, hemostasis, and immunity (12).

METABOLISM OF INTESTINAL AND HEPATIC-DERIVED TGRLS

Chylomicrons are intestinal-specific lipoproteins, formed mainly in the jejunum after a meal. Owing to the large TG core (>90%), chylomicron density is <1.006 g/ml, but they are heterogeneous, ranging from 75 to 1,200 nm in diameter. They also contain a small amount of cholesteryl esters, 1 structural protein, apoB48, and minor exchangeable apolipoproteins.

Dietary TG are hydrolyzed in the stomach and proximal small intestine to form fatty acids and 2-monoacylglycerol (**Central Illustration**, top) (13). Enterocytes absorb these lipids through either passive

CENTRAL ILLUSTRATION **Intestinal Synthesis and Hepatic Synthesis and Metabolism of TGRLs**



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(Top) Key pathways regulating intestinal synthesis and metabolism of triglyceride-rich lipoproteins (TGRLs) are illustrated (see the text for details of this pathway and its genetic regulation). **(Bottom)** Key pathways regulating hepatic synthesis and metabolism of TRGLs are illustrated (see the text for details about this pathway and its genetic regulation). ANGPTL3 = angiopoietin-like protein 3; Apo = apolipoprotein; DGAT = diglyceride acyltransferase; ER = endoplasmic reticulum; FA = fatty acid; HSPG = heparin sulfate proteoglycan; GHIHBP1 = glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LDL = low-density lipoprotein; LDL-R = low-density lipoprotein receptor; LPL = lipoprotein lipase; LRP1 = low-density lipoprotein receptor-related protein; MG = monoglyceride; MGAT = monoglyceride acyl transferase; MTP = microsomal transfer protein; NPLC1L1 = Niemann-Pick C1 like; PCSK9 = proprotein convertase subtilisin kexin type 9; PCTV = pre-chylomicron transport vesicle; TG = triglyceride; VLDL = very low-density lipoprotein; VTV = very low-density lipoprotein transport vesicle.