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Triglyceride-Rich Lipoprotein Remnant Particles and Risk of Atherosclerosis

Howard N. Hodis, MD

More than 3 decades of clinical research have suggested a relationship between triglycerides and coronary heart disease. However, because of the complexity of what is actually measured by a plasma triglyceride determination, establishing a firm relationship between triglycerides and coronary heart disease has been difficult. Triglycerides are carried in virtually all plasma lipoproteins and present a different risk profile in both the fasting and postprandial states, making triglyceride-rich lipoproteins highly heterogeneous. This heterogeneity is a major contributing factor to the complexity of the relationship between triglycerides and coronary heart disease.

See p 2858

Accumulating evidence indicates that specific triglyceride-rich lipoprotein remnants of differing size and composition, such as VLDL, IDL, lipoprotein B–containing particles (LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E), and markers of triglyceride-rich lipoprotein metabolism such as apolipoprotein C-III (apoC-III), are more related to progression of triglyceride-rich lipoprotein metabolism such as apolipoprotein (LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E), and markers of triglyceride-rich lipoprotein metabolism such as apolipoprotein C-III (apoC-III), are more related to progression of atherosclerosis than triglycerides per se. 2

In this issue of Circulation, Kugiyama et al 3 present further evidence for the relationship between coronary heart disease and triglyceride-rich lipoproteins, demonstrating in patients with coronary artery disease that remnant lipoprotein levels in the fasting state predict future clinical coronary events independently of other risk factors. This is an important observation because it is consistent with a previous report that showed that calculated IDL plus estimated remnant VLDL as a measure of triglyceride-rich lipoprotein remnants was significantly correlated with the progression of coronary artery disease and clinical coronary events. 4

The assertion by Kugiyama et al 3 that fasting remnant lipoproteins may reflect postprandial remnant lipoproteins is consistent with the long circulatory residence time of certain partially delipidized lipoproteins and their contribution to atherosclerosis. Remnant lipoproteins are partially catabolized chylomicrons and VLDLs that are reduced in size, partially depleted of triglycerides, and enriched with cholesterol esters. Remnants formed from catabolism of VLDL consist of smaller VLDLs and IDL.

Triglyceride-rich lipoproteins comprise a great variety of nascent and metabolically modified lipoprotein particles differing in size, density, and lipid and apolipoprotein composition. Although the exact physical-chemical composition of an atherogenic lipoprotein is not known, evidence indicates that size and specific structural arrangement of lipids and apolipoproteins are the main factors determining atherogenicity. Studies have consistently shown an inverse relationship between lipoprotein particle size and capacity for lipoproteins to enter the arterial wall. Accordingly, chylomicrons and large VLDLs (Svedberg flotation unit [Sf] 60 to 400) do not seem capable of entering the arterial intima. On the other hand, small VLDLs (Sf 20 to 60) and IDLs (Sf 12 to 20) seem to share a similar mechanism and potential for penetrating the arterial intima. As such, certain triglyceride-rich lipoproteins are atherogenic, whereas others are not. In particular, small VLDLs and IDLs have been shown to be independently associated with the presence, severity, and progression of atherosclerosis. 4-10

Serial arterial imaging studies have provided an excellent opportunity to extend cross-sectional associations between triglycerides and coronary heart disease to studies that permit the examination of the relationships between triglyceride-rich lipoproteins and the progression of atherosclerosis. In a subgroup analysis of lipoprotein mass concentrations measured by analytical ultracentrifugation at baseline and after 2 years in the Type II Coronary Intervention Study, change in IDL mass (Sf 12 to 20) was significantly predictive of coronary artery lesion progression at 5 years. 5 With the same analytical ultracentrifugation methodology, lipoprotein mass concentrations were measured at baseline and every 6 months for 2 years in 220 subjects participating in the Monitored Atherosclerosis Regression Study (MARS). 6 Lipoproteins in the Sf 12 to 60 range (IDLs and small VLDLs) emerged as the independent correlates of coronary artery atherosclerosis progression.

In the same MARS cohort, apoC-III in the LDL-VLDL subfraction was also found to be significantly correlated with coronary artery lesion progression. 11 ApoC-III is a marker of triglyceride-rich lipoprotein metabolism and clearance of VLDLs and chylomicrons. 12 Inhibition of lipoprotein lipase–activated lipolysis by VLDL-associated apoC-III prolongs the circulatory residence time of VLDL and therefore increases the exposure time of the arterial wall to this atherogenic particle. ApoC-III in VLDL is associated with denser, smaller VLDL subclasses believed to be particularly atherogenic. 13 In a randomly selected subgroup of 63 subjects, lipoprotein...
particles were isolated by column immunooaffinity techniques. Subjects with coronary artery lesion progression had significantly higher levels of LP-B, a summed measure of triglyceride-rich lipoproteins) and LP-A-II:B:C:D:E particles of small VLDL and/or IDL-like sizes. LP-A-II:B:C:D:E is a specific triglyceride-rich lipoprotein particle with a low affinity for lipoprotein lipase and a long circulatory residence time that most likely contributes to its atherogenicity. The 3 independent techniques for identifying triglyceride-rich lipoproteins outlined above are based on different physical-chemical properties: protein composition (electrophoresis), lipoprotein mass (analytical ultracentrifugation), and lipoprotein particles (column immunooaffinity). These results provide compelling evidence for the relationship between the progression of coronary artery atherosclerosis and triglyceride-rich lipoprotein remnants. Other studies, such as the Cholesterol Lowering Atherosclerosis Study and the Program on the Surgical Control of the Hyperlipidemias, have also demonstrated a relationship between coronary artery lesion progression and apoC-III and VLDL, respectively. The aforementioned findings have a particular importance in that triglyceride-rich lipoproteins such as small VLDLs and apoC-III are related to the progression of mild/moderate (<50% diameter stenosis) rather than severe (≥50% diameter stenosis) coronary artery lesions. This is relevant to the findings of Kugiyama et al because coronary artery lesions of <50% diameter stenosis appear to be the lesions that predict clinical coronary events. Triglyceride-rich lipoproteins may contribute to lesion progression, plaque rupture, and clinical coronary events through a variety of mechanisms. Triglyceride-rich lipoproteins are susceptible to peroxidative damage, can be taken up by macrophages directly without oxidative modification to produce foam cells, and are intimately associated with the clotting and fibrinolytic pathways, thus linking atherosclerosis and thrombosis.

Results from the Bezafibrate Coronary Atherosclerosis Intervention Trial and the Lopid Coronary Angiographic Trial, randomized serial coronary angiographic clinical trials that tested bezafibrate and gemfibrozil, respectively, support the growing evidence for the relationship between triglyceride-rich lipoproteins and atherosclerosis. In these trials, a reduction in triglycerides with essentially no change in LDL-cholesterol levels resulted in a reduction in the progression of coronary artery atherosclerosis in both native arteries and aortocoronary bypass grafts to a similar degree as LDL-cholesterol lowering with the HMG-CoA reductase inhibitors. These studies suggest that triglyceride-rich lipoprotein reduction by fibric acid derivatives, perhaps through the downregulation of apoC-III gene expression and reduction in VLDL-associated apoC-III levels, results in the reduction of atherosclerosis progression. The accumulated literature has consistently indicated triglyceride-rich lipoprotein remnants to be a risk factor for the progression of atherosclerosis and presents plausible mechanisms by which these lipoproteins may be atherogenic and result in clinical coronary events. Small VLDL, IDL, apoC-III, and lipoprotein B–containing particles measured in the fasting state most likely represent specific remnant lipopro-

References


**Key Words:** Editorials: ■ atherosclerosis ■ lipoproteins ■ risk factors