Editorial Comment

Role of Triglyceride-Rich Lipoproteins in Progression of Atherosclerosis

Richard J. Havel, MD

Many studies have identified low density lipoprotein (LDL) cholesterol as a predictor of coronary heart disease (CHD), assessed clinically or from coronary artery narrowing, detected angiographically. In recent years, evidence has shown that reducing LDL cholesterol levels by dietary means alone or together with drug treatment reduces the rate at which coronary narrowing progresses. Ways to drastically reduce LDL cholesterol levels have been available for the last decade, and the Cholesterol-Lowering Atherosclerosis Study (CLAS) was among the first to apply such an intervention to small groups of subjects with advanced coronary atherosclerotic disease. The CLAS investigators determined the effect of a potent combined drug regimen in men who had coronary artery bypass grafting, which permitted an evaluation of the course of disease in bypassed as well as native vessels.

The combined regimen of colestipol, a bile acid-binding resin that increases the rate of catabolism of LDL by upregulating hepatic LDL receptors, and nicotinic acid, which is thought to reduce the rate of synthesis of very low density lipoproteins (VLDL), the precursor of LDL, lowers LDL cholesterol levels by as much as 50% in compliant patients. In the CLAS, the actual reduction was from 171 to 97 mg/dl (43%). In addition, however, the level of plasma triglycerides was reduced from 151 to 110 mg/dl (27%) and that of high density lipoprotein (HDL) cholesterol was increased from 45 to 61 mg/dl (36%). Thus, the concentration of all major lipoprotein classes is altered substantially by this regimen.

Although in cross-sectional studies of men with premature CHD plasma triglycerides as well as LDL cholesterol levels are almost invariably increased, the “atherogenicity” of plasma triglycerides has remained controversial, mainly because in most prospective studies triglycerides have failed to survive the test of multivariate analysis as an independent risk factor. In particular, when matched against the level of HDL cholesterol, an association between CHD endpoints and triglycerides has been found mainly in Sweden and in older women in the Framingham Study in the United States. Nonetheless, many students of the relation between triglycerides and atherogenesis have been reluctant to conclude that triglycerides are not important as an index of atherosclerotic risk because risk is increased in some genetic disorders associated with elevated VLDL triglyceride levels and because some species of VLDL (particularly those enriched in cholesterol and apolipoprotein E) are readily taken up into macrophages, converting them into foam cells in vitro. In addition, the application of multivariate analysis to the highly interrelated lipoprotein-lipid transport system has been criticized. Plasma triglycerides are the single most important predictor of HDL cholesterol level in cross-sectional studies. When plasma triglyceride catabolism is efficient, and plasma triglyceride levels are low, HDL cholesterol levels tend to be high. As triglyceride levels increase within the normal range, HDL cholesterol levels fall almost exponentially. The fall reflects both a progressively smaller average size of HDL particles and a replacement of cholesterol with triglycerides within the HDL core.

In this issue of Circulation, the relation in the CLAS study between levels and ratios of plasma lipoprotein lipids and apolipoproteins and the progression of coronary narrowing in native vessels and bypass grafts is reported for both drug-treated patients and those assigned to a placebo group. The results in the placebo group are as interesting as in those treated with colestipol and nicotinic acid. When divided into 49 “progressors” and 33 “nonprogressors,” according to global angiographic change after 2 years, HDL cholesterol levels were identical, but those of LDL cholesterol were lower by 24 mg/dl (8%) in the nonprogressors and those of VLDL cholesterol (calculated by a formula) were lower by 8 mg/dl (26%). Plasma triglycerides were lower by 29 mg/dl (25%) in nonprogressors. All these differences were statistically significant by univariate analysis. Among 16 variables tested in the drug-treated group, the concentration of apolipoprotein (apo) C-III that was

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See p 470
not precipitated with LDL and VLDL by heparin was significantly different on univariate analysis. The value, thought to reflect the amount of this protein associated with HDL particles, was 17% higher in nonprogressors.

After multivariate analysis, only the concentration of non-HDL cholesterol (cholesterol associated with VLDL and LDL) was a significant predictor of disease progression in the placebo group, and the level of apo C-III associated with HDL was the only significant predictor in the drug-treated group. The investigators concluded that the drug treatment overrode the effects of most pretreatment risk factors. Since drug treatment did not affect the level of apo C-III in whole plasma, they postulate that the level of this protein in HDL, or perhaps the ratio of apo C-III associated with HDL to that associated with VLDL and LDL, is a measure of the efficiency of triglyceride transport (the C-III ratio was highly correlated with that of plasma triglycerides as well as HDL cholesterol in both the placebo and drug-treated groups). The authors provide arguments to bolster this thesis based on observed metabolic effects of apo C-III.

Apo C-III is one of three apolipoproteins of low molecular weight that are associated mainly with VLDL and HDL in plasma (the other two are apo C-I and apo C-II). Only the function of apo C-II has been established unequivocally as an essential cofactor for the rate-limiting enzyme of plasma triglyceride metabolism, lipoprotein lipase.12 Apo C-I and apo C-III, in vitro, can inhibit the “activation” of lipoprotein lipase by apo C-II,13 and in patients lacking apo C-III genetically, plasma triglyceride catabolism appears to be accelerated.14 All the C apoproteins, including apo C-III, also inhibit the uptake by the liver of partially lipolyzed triglyceride-rich lipoproteins (VLDL and chylomicron “remnants”).15 Thus, removal of apo C-III from VLDL and chylomicrons and their remnants may promote both the removal of triglycerides from these lipoproteins by lipoprotein lipase and the uptake of the resulting remnant particles by the liver.

HDL constitute a reservoir of C apoproteins that cycle repeatedly between triglyceride-rich lipoproteins and HDL as plasma triglycerides are catabolized.16 In the postabsorptive steady state, the distribution of C apoproteins between VLDL and HDL reflects the relative concentration of these two lipoprotein populations. Under many, but perhaps not all, conditions, this distribution (reflected by the apo C-III ratio as measured in the CLAS study) is an index of the rate at which VLDL triglycerides are catabolized. However, the distribution of apo C-III is not unique. For example, the ratio of VLDL triglycerides to HDL cholesterol also reflects in general the rate of plasma triglyceride catabolism. Possibly, the apo C-III ratio is a better reflection of the rate of catabolism of those triglyceride-rich lipoproteins that are enriched in cholesterol and apolipoprotein E (i.e., VLDL remnants).

The CLAS study provides additional support for the hypothesis that at least some classes of VLDL are atherogenic. In another recent intervention trial, the Helsinki Heart Trial,17 the effect of gemfibrozil on CHD risk was assessed in middle-aged men. Like the drug combination used in CLAS, gemfibrozil reduces VLDL and raises HDL levels and, except in persons with moderate to severe hypertriglyceridemia, reduces LDL levels. The positive outcome of the Helsinki Trial has been interpreted not only to provide additional support for the importance of LDL lowering in reducing CHD risk, but also for the possible importance of raising HDL levels as well. As pointed out elsewhere,5 the reduction of plasma triglycerides (hence, VLDL levels) produced by gemfibrozil in the Helsinki Heart Trial was more pronounced than the elevation of HDL cholesterol. Furthermore, the subset of patients with type IV and type IIB hyperlipoproteinemia who had little or no reduction of LDL levels but the greatest absolute reduction of VLDL levels had the most favorable outcome.

The current approach to assessment of CHD risk by lipoprotein analysis is based on measurement of total plasma cholesterol and triglycerides and HDL cholesterol. LDL cholesterol is estimated by a formula, as is the level of VLDL cholesterol or triglycerides. There is a critical need for methods to quantify the concentration of “atherogenic” species of triglyceride-rich lipoproteins. Such methods might include measuring the concentration of VLDL remnants that have been acted on by lipoprotein lipase but not yet taken up in the liver. Application of such measurements to trials such as the CLAS and the Helsinki Heart Trial could provide a more direct assessment of the atherogenicity of triglyceride-rich lipoproteins and the VLDL-HDL nexus.

References
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