Cardiologists and clinicians have in general accepted the significance of a raised plasma cholesterol concentration. Doubters notwithstanding, most cardiologists will advise cholesterol-lowering measures if low density lipoprotein (LDL) levels are high, particularly in the presence of other risk factors for cardiovascular disease. Most would also agree that risk must be maximally reduced after coronary artery bypass grafting or angioplasty. Clinicians have also come to recognize the need to take into account the concentration of high density lipoprotein (HDL).

See p 495

While becoming aware of other terms such as hyperapobetalipoproteinemia, intermediate density lipoprotein (IDL), “dense LDL,” and so on, cardiologists have probably not anticipated the possibility that these factors may be superior predictors of risk. Nor are they satisfied about the clinical significance of hypertriglyceridemia, despite the fact that the plasma triglyceride level is among the most common measurements in clinical chemistry.¹

In this issue of Circulation, Austin and collaborators² report on an apparently very prevalent lipoprotein phenotype, carrying a probable high risk for atherosclerosis,³ and focus on the significance of raised triglyceride, IDL, HDL, and dense LDL. The remarkable aspects of this study of 301 subjects from 61 families is that this complex phenotype may be inherited as a single gene trait and appears to be very common. Of immediate practical significance is that this important phenotype may be recognized by measuring the plasma triglyceride and HDL cholesterol levels alone. However, the authors' suggestion that other common abnormal phenotypes such as hyperapobetalipoproteinemia or simpler variations in lipid and apolipoprotein levels (e.g., raised triglyceride and low HDL) are partial expressions of this single gene may be premature. LDL are polymorphic, that is, there are several subclasses of LDL differing in size and in the lipids carried within the core. In normal subjects, the predominant class is large and carries more cholesterol than the smaller, denser LDL found in increased amounts in some lipid disorders. Dense LDL characterize hypertriglyceridemia⁴ and hyperapobetalipoproteinemia.⁵ Despite normal plasma total cholesterol and LDL cholesterol concentrations, subjects with hyperapobetalipoproteinemia are at increased risk for atherosclerosis.⁵

Austin et al² have distinguished two phenotypes based on the nature of the predominant LDL particle: phenotype A, the larger LDL, and phenotype B, the denser cholesterol-depleted LDL. Phenotype B was associated with the other lipoprotein abnormalities (raised triglyceride, IDL, and apolipoprotein B and low HDL and apolipoprotein A-I). It should be noted that plasma total cholesterol is not necessarily raised in this phenotype. The expression of phenotype B defined by the nature of the LDL particle and based on single gene inheritance was found to be as high as 44% in adult men and postmenopausal women.⁶

Although this particular population of Mormons was not selected for a history of cardiovascular disease, each of the abnormalities associated with phenotype B carries increased cardiovascular risk. In these healthy families, phenotype B could be differentiated from the benign phenotype A, in the majority, on the basis of plasma triglyceride and HDL cholesterol concentrations. A value of 95 mg/dl for triglyceride discriminated the two phenotypes in 83% of subjects, whereas 39 mg/dl for HDL cholesterol discriminated less well, with 28% of A phenotypes being below this level.

This phenotype, named by the authors as an atherogenic lipoprotein phenotype, must be distinguished from familial combined hyperlipoproteinemia (FCHL). FCHL is commonly associated with premature coronary heart disease⁴; it is also characterized by increased triglyceride and apolipoprotein B levels and low HDL cholesterol. Although the plasma cholesterol concentration is generally raised, this is not invariably; when dense LDL predominates,
then the FCHL phenotype differs little from that reported by Austin et al.2

It should be noted that both the above phenotypes, which appear to confer a high risk for atherosclerosis, have raised triglyceride levels as a feature. In fact, recent studies of near blood relatives of individuals with premature coronary heart disease show how often hypertriglyceridemia occurs as part of abnormal lipoprotein phenotypes.7 Hypertriglyceridemia with low HDL, or as part of FCHL or with hyperapoB-apoE-proteinemia, is found more often than familial hypercholesterolemia.

This has been one factor in the reawakening interest in plasma triglyceride as an independent risk factor. Other factors have been reviewed recently elsewhere.1,4

Case-control comparisons of younger myocardial infarction survivors had generally shown higher triglyceride levels in the affected subjects.8,9 The familial aggregation of different hyperlipoproteinemias around post-myocardial infarction patients demonstrated the frequency of familial hypertriglyceridemia.10,11 Prospective studies in Scandinavia had shown that plasma triglyceride levels were independently related to future coronary artery disease.12

In an Australian study, the severity of coronary atherosclerosis, judged by coronary arteriography, was related independently to plasma triglyceride and IDL concentrations in women.13 This gender difference is interesting because plasma triglyceride showed greater predictive power in women than in men, both in the Framingham study14 and in a Swedish prospective study.15 The association between severity of coronary atherosclerosis and IDL levels has been observed in two other studies.16,17 Furthermore, the IDL concentration was strongly and independently predictive of future coronary atherosclerosis in the National Heart, Lung, and Blood Institute's Type 2 Coronary Intervention Study.18

IDL are remnants of the catabolism of triglyceride transporting very low density lipoprotein (VLDL). These smaller triglyceride-containing lipoproteins are also relatively enriched in cholesterol and can deliver lipids to the cellular components in a developing atheroma, the smooth muscle cells, and macrophages.

Hypertriglyceridemia is not a single entity, and the metabolic disturbance that leads to hypertriglyceridemia in one individual may be quite different from that occurring in another. What is common, however, is the complex interrelation between triglyceride-rich lipoproteins and LDL and HDL. The dismantling of VLDL leads to the formation of LDL and exchange and transfer of lipids and apolipoproteins among the major lipoprotein classes. These complexities appear to have exceeded the capacity of the statistical models that have led epidemiologists to discount the significance of hypertriglyceridemia. Those analyses had suggested, possibly erroneously, that any association between triglyceride and coronary heart disease merely reflected the metabolic link between triglyceride and HDL. This view is being revised.14,19

An equally valid explanation for the apparently weaker correlation between triglyceride and coronary heart disease is that the heterogeneity of triglyceride particles masks those that are indeed atherogenic. Further, the far greater day-to-day variation in plasma triglyceride than in LDL or HDL levels would reduce the power of a single triglyceride measurement to predict future disease.

Two intervention studies, one with diet20 and the other with gemfibrozil (Helsinki Heart Study),21 are also consistent with a link between plasma triglyceride and coronary disease. In the former,20 (Leiden Intervention Trial), progression of coronary atherosclerosis correlated positively with VLDL cholesterol and triglyceride and negatively with HDL cholesterol. In the gemfibrozil trial,21 reduction in clinical events was associated with an approximately 40% decline in plasma triglyceride, although its significance was excluded when the rise in HDL was taken into account.

It has recently been shown22 that familial hypertension may also be associated with either the fully expressed or a partially expressed lipoprotein phenotype resembling that reported by Austin et al.2 This has been named familial dislipidemic hypertension.

Austin and coworkers have done well to establish the frequency of this complex lipoprotein phenotype. It emphasizes the need to consider the several manifestations of this disturbance as reflecting the interrelations among the lipoproteins. To dismiss an association between coronary heart disease and one class of lipoprotein on statistical grounds ignores the fact that this may not be the way arteries see it.

References
7. Schaefer EJ: Genetic HDL disorder and premature coronary disease, in Drugs Affecting Lipid Metabolism. 1990 (in press)

*(Circulation 1990;82:649–651)*
New lipoprotein profiles and coronary heart disease. Improving precision of risk.
P J Nestel

Circulation. 1990;82:649-651
doi: 10.1161/01.CIR.82.2.649
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/2/649.citation