Familial combined hyperlipidemia (FCH) was originally identified as a new phenotype in studies of survivors of myocardial infarctions and their relatives. Patients with FCH were found to present with any of three patterns of lipoprotein distribution: elevated plasma levels of very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL) or both. Within kindred, affected individuals often present with different lipoprotein patterns that tend to change over time; most patients manifest the combined pattern at some time. The phenotype also shares some features with dyslipidemic hypertension and the metabolic syndrome. Affected family members tend to display elevated serum apolipoprotein (apo) B levels; in FCH, most studies report an approximate doubling of the secretion rate for apoB-100. The content of intermediate-density lipoproteins (IDL) is usually elevated as well. Of particular interest is the reduced high-density lipoprotein (HDL) cholesterol mass, due in part to the increased movement of cholesteryl esters from HDL particles to triglyceride-rich lipoproteins with increasing plasma triglycerides. This is mediated by cholesteryl ester transfer protein (CETP) and is consistent with a shift of LDL to smaller diameters.

Allayee and colleagues report in this issue of Circulation Research the results of their study of apoA-II levels in families with FCH to determine whether the HDL-associated protein could play a role in the pathogenesis of this common lipid disorder. Their results suggest that plasma apoA-II variation is associated with certain traits that are altered in FCH, providing circumstantial evidence for a potential genetic component for this association. Whereas FCH patients present with either hypertriglyceridemia or hypercholesterolemia or both, a significant number also exhibit several metabolic perturbations associated with insulin resistance. Although the metabolism of HDL is not completely understood, there is increasing clinical evidence and fundamental research to support the significant antiatherogenic role of HDL. HDL has multiple functions within the body, including reverse cholesterol transport, providing the cholesterol substrate for bile acid synthesis, prevention of lipoprotein oxidation, selective uptake of cholesterol by steroidogenic cells, and resistance to pathogens. HDL protects against the development of atherosclerosis both through its role in reverse cholesterol transport and by impeding LDL oxidation, an essential mechanism in atherogenesis. ApoA-II, predominantly synthesized in the liver, is its second major protein component. ApoA-II may displace apoA-I from the surface of HDL, thereby reducing the capability of the particles to act as substrate for lecithin:cholesterol acyltransferase (LCAT). The decrease in LCAT activation and the subsequent inhibition of reverse cholesterol transport is thought to give apoA-II proatherogenic properties. The functions of apoA-II include modulating the structure and function of HDL by influencing hepatic lipase-mediated lipolysis, analogous to apoC-III in the lipolysis of VLDL by lipoprotein lipase (LpL). ApoA-II also modulates the antiinflammatory and antioxidant properties of HDL, in part due to its displacement of paroxonase (PON). To this point, however, in an independent human apoA-II transgenic (huApoAII-Tg) model, the basal oxidation of lipoproteins was not increased. HDL of transgenic mice protected VLDL from oxidation more efficiently than HDL of controls. While this function depended in part on the ratio of apoA-I to apoA-II, the resulting decrease in both PON and platelet-activating factor acetyl hydrolase activities in huApoAII-Tg mice is best explained by their lower plasma HDL levels; the unchanged basal lipoprotein oxidation in transgenic mice suggests that huApoAII-rich HDL may maintain adequate antioxidant potential. However, the effects of hypertriglyceridemia, per se, on HDL are significant, reflecting transfer of cholesterol esters to VLDL and a reverse transfer of triglyceride to HDL. This creates additional HDL substrate for hepatic lipase and thus could result in an increase in the population of small apoA-II–bearing HDL particles, which may have a significant effect on the molecular speciation of HDL. Generation of the atherogenic species, small/dense HDL, is a direct result of elevated triglycerides. The decrease in HDL cholesterol and in LDL size is mediated in part by hepatic lipase activity and was observed previously in this FCH study population.

The three major lipoprotein abnormalities observed in the metabolic syndrome are increased fasting and postprandial triglyceride-rich lipoproteins, decreased HDL, and a shift to small, dense LDL particles. Insulin resistance and the resulting hyperinsulinemia lead to hypersecretion of VLDL. The increase in small, dense LDL particles and the decrease in large buoyant HDL particles are due to the cholesterol ester transfer protein-mediated enrichment of triglyceride-rich lipoproteins with cholesteryl esters. This results in a depleted
HDL substrate pool. This mechanism is likely the same in FCH. Insulin resistance is often seen in patients with FCH and is associated with impaired suppression of lipolysis by hormone-sensitive lipase in adipocytes, producing an increased flux of free fatty acids to the hepatocyte, culminating in increased synthesis of VLDL. Insulin resistance, which also diminishes LpL activity, would amplify the extent of hypertriglyceridemia. Obesity is observed in patients with FCH, independent of insulin resistance, which would contribute further to hyperlipidemia. Increased insulin concentrations are associated with the phenotype of smaller-diameter HDL particles, but not with concentrations of apoA-I or apoA-II. This suggests the existence of genes, which pleiotropically influence variation in both HDL and insulin levels, contributing to the clustering of proatherogenic traits in insulin resistance states. Patients with type 1 diabetes have greatly increased phospholipid transfer protein (PLTP) activity and altered HDL subclass distribution. Higher PLTP activity is associated with an increase in large HDL and a shift of apoA-I into the apoA-I:A-II HDL subfraction. PLTP is also positively associated with apoB, and total VLDL and IDL particle number. Reservations in the interpretation of this in human beings are in order, given the difference in lipoprotein metabolism between these two species. In humans, fenofibrate significantly decreased plasma triglyceride and VLDL apoB and elevated HDL cholesterol, HDL cholestrol, apoA-I, and apoA-II concentrations, but it did not significantly alter LDL cholesterol.

The “atherogenic” status of apoA-II remains equivocal; the impaired antioxidant capability observed in huApoAI-Tg versus huApoAI-Tg mice, due in part to decreased association of PON, might be a trade-off for another role—perhaps one of several now recognized in the body’s innate immune defense. Thus, an increased content of apoA-II could ensure a subfraction of HDL that is available for a process that might be a more important concern to primal humans than an overabundance of energy. A potential explanation for the proatherogenic profile of apoA-II transgenic models is that overexpression of apoA-II causes accumulation of an apoA-I:A-II HDL population at the expense of the apoA-I:HDL subfraction, rendering it less able to remodel triglyceride-rich lipoproteins, which in turn increases residence time of atherogenic lipoproteins, accelerating atherosclerosis. Taken together, other demands on HDL might be dictating lipoprotein metabolism.

The evidence for association of apoA-II levels in FCH indicates that it is likely not a primary genetic determinant, as evidenced in the lack of a major linkage to this region in previous studies. The effect of triglyceride-rich lipoprotein metabolism on the molecular speciation of HDL could readily explain the cosegregation of apoA-II levels with triglycerides in this study. It is interesting to note that, with the exception of the linkage on chromosome 5q, there was no evidence of linkage with HDL-cholesterol levels coincident with the apoA-II levels reported by Allayee and colleagues. A spontaneous mouse strain displaying many of the metabolic features of human FCH identified by the same group was found not to involve the apoA-II gene locus that was adjacent to the initial linkage result. The emerging view is that FCH is multigenic, with a complex pattern of inheritance involving a number of primary and modifying genes.

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