Apoproteins B and A-I and Coronary Artery Disease in Humans

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This review initially will consider the association between premature coronary artery disease and abnormal lipoprotein cholesterol levels, but then focus on recent evidence linking the apoproteins of lipoproteins to atherosclerosis. This evidence suggests that although cholesterol is the major component common to the plasma and the arterial wall, plasma apoproteins may serve as a better marker of risk for atherosclerosis.

Hyperlipidemia

The association between serum cholesterol levels and atherosclerosis in humans was suggested when Thannhauser and Muller in 1938 each demonstrated familial aggregation of individuals with tendon xanthomata, hypercholesterolemia, and coronary artery disease (CAD). The association was generalized by studies such as those in Framingham which demonstrated that the risk for coronary artery disease rose over the entire range of serum cholesterol. This relation was seen predominantly in those persons 30 to 49 years of age at entry into the study and most markedly in those 30 to 39 years old. Different lipoproteins affect risk differently. Among subjects 49 years and older, low density lipoprotein (LDL) cholesterol was associated with moderate CAD risk, as had been suggested earlier by Gofman et al.; however, in these older individuals, the high density lipoprotein (HDL) cholesterol level seemed to have greater inverse predictive value. Decreased HDL cholesterol also was shown to be associated with CAD risk in younger people. And finally, elevated triglyceride levels have been linked with CAD but may not be independent of the effect of other lipoproteins or of obesity. In spite of the fact that CAD risk varies over the entire range of plasma concentrations of LDL cholesterol and HDL cholesterol, clinically only those with levels at the 5% extremes of the population usually are labeled abnormal, while others with milder differences from population norms have been considered normal.

Hyper-B-Apoproteinemia

Alaupovic was the first to suggest that apoproteins should be considered when evaluating lipoprotein disorders, and in the early 1970s several groups demonstrated elevations in plasma and LDL and/or very low density lipoprotein (VLDL) apo B levels in patients with most types of hyperlipidemia. Lees and others noted protein enrichment of LDL in some subjects with hypertriglyceridemia and were the first to suggest that LDL composition was heterogeneous in persons with lipoprotein phenotype IV; while all type IV subjects had LDL cholesterol levels in the normal range, some subjects had elevated LDL apo B levels. In 1978 Avogaro et al. found that total plasma apo B levels were elevated in individuals with CAD regardless of whether they were normocholesterolemic or hypercholesterolemic. Vergani et al. and others also found higher plasma apo B levels in subjects with atherosclerosis than those apparently free of atherosclerosis. Indeed, higher plasma apo B levels were reported in persons with CAD compared to those without CAD, both in those with lipoprotein phenotypes IIa, IIb, and IV as well as those with normal lipid levels.

Sniderman et al. measured apo B levels in LDL separated from VLDL by exclusion gel radial immunodiffusion or by preparative ultracentrifugation.
They separated their subjects according to LDL cholesterol level above or below 200 mg/dl. The few subjects with elevated LDL cholesterol levels were noted to have cholesterol-enriched LDL with elevated LDL cholesterol/apo B ratios. Among those with CAD diagnosed by angiography with normal LDL cholesterol levels (less than 200 mg/dl), Sniderman et al. noted elevated LDL apo B and, thus, cholesterol-depleted LDL. They termed this entity, characterized by 1) LDL cholesterol below 200 mg/dl, 2) elevated LDL apo B, and 3) low LDL cholesterol/apo B ratio, "hyperapobetalipoproteinemia" to contrast it with lipid phenotypes IIA and IIB (Figure 1).

Sniderman et al. subsequently found that some subjects with hypertriglyceridemia with phenotype IV also had hyperapobetalipoproteinemia. In survivors of myocardial infarction, 81% of those with hypertriglyceridemia had elevated LDL apo B levels, while 70% of those with normal triglyceride and cholesterol levels had elevated LDL apo B levels. In a group of subjects selected for hypertriglyceridemia (type IV), atherosclerosis was more prevalent among those with elevated LDL apo B levels, as Lees and Schonfeld et al. had originally speculated. Onitri and Jover also found elevated LDL apo B levels in subjects with CAD. In addition, they noted that subjects with CAD had higher than normal VLDL apo B levels. Avogaro et al. also observed elevated LDL apo B levels in CAD subjects matched for total cholesterol and triglyceride levels with controls. These researchers were unable to demonstrate elevated VLDL apo B levels, but did note elevated intermediate density lipoprotein (IDL) apo B in subjects with CAD. Like Sniderman et al., Avogaro et al. noted protein enrichment of LDL in patients with CAD, a phenomenon first reported in 1963 by Cramer.

The classification of lipid phenotype by the measurement of lipoprotein lipids implies that only those with lipid levels above the 95th percentile are abnormal. The concept of hyperapobetalipoproteinemia implies that those who have lipoprotein lipid levels below the 95th percentile but higher than the mean value for a population and also have elevated LDL apo B concentrations, have increased risk for developing CAD.

One can use both lipoprotein lipids and protein to assess CAD risk (Figure 1). Apo B is present in VLDL, IDL, and LDL. Individuals with elevated plasma apo B levels, hyper-B-apoproteinemia, can be divided into two groups, those with elevated LDL cholesterol (phenotypes IIA and IIB) and those with LDL cholesterol below some cutpoint, such as the 95th percentile. Individuals with familial hypercholesterolemia, with an apo B receptor defect, and often tendon xanthomata, have hypercholesterolemia with cholesterol enrichment of LDL. Most individuals with elevated levels of apo B, however, do not have this autosomal dominant disorder. Among those with normal LDL cholesterol levels but elevated LDL apo B values (hyperapobetalipoproteinemia), there are some with elevated VLDL levels (phenotype IV) and others with normal triglyceride levels (and, thus, a normal lipid phenotype). These hypertriglyceridemic and normallipidemic individuals with apparent increased CAD risk can be identified by the elevated LDL apo B levels. Avogaro et al. also observed elevated LDL apo B levels in CAD subjects matched for total cholesterol and triglyceride levels with controls. These researchers were unable to demonstrate elevated VLDL apo B levels, but did note elevated intermediate density lipoprotein (IDL) apo B in subjects with CAD. Like Sniderman et al., Avogaro et al. noted protein enrichment of LDL in patients with CAD, a phenomenon first reported in 1963 by Cramer.

Some subjects with phenotypes IIA and IIB and some with hyperapobetalipoproteinemia may have familial combined hyperlipidemia (FCHL), originally described by Goldstein et al. and Nikkila and Aro. In FCHL, elevated apo B levels appear to be due
to increased synthesis, since overproduction of both VLDL apo B and LDL apo B have been documented. Such individuals have the same abnormalities in LDL composition as were described by Sniderman et al., in that their LDL apo B levels are elevated with a relatively low LDL cholesterol/apo B ratio. In both familial combined hyperlipidemia and hyperapobetalipoproteinemia, variable hyperlipidemia has been observed. That is, individuals may have a different lipid phenotype on different occasions (IIb, IV, and possibly IIA) and can often have all lipoprotein lipid levels below the 95th percentile while the LDL B protein, however, remains elevated. Familial combined hyperlipidemia is a genetic derangement in lipoprotein metabolism; hyperapobetalipoproteinemia describes a phenotype, not a genotype. At the moment, it is not known how many of the individuals with hyperapobetalipoproteinemia or how many individuals with type IIA and IIB who do not have familial hypercholesterolemia have FCHL. The answer is crucial, of course, to assessing the genetic impact on coronary disease, since Goldstein et al. suggested a minimum prevalence of 11% for FCHL in myocardial infarction survivors under the age of 60 years, while Sniderman et al. suggested that as many as 50% to 80% of individuals with CAD have hyperapobetalipoproteinemia. What portion of patients with variable lipid phenotypes, polygenic hypercholesterolemia, or sporadic hypertriglyceridemia have FCHL or hyperapobetalipoproteinemia remains undefined. In addition, and of particular importance, almost nothing is known of the environmental influences, such as drugs and diet on LDL B protein levels.

HDL Apoproteins

Among the groups of individuals mentioned earlier, variability in HDL mass and composition also has to be considered when assessing risk for CAD. For example, in familial hypercholesterolemia HDL cholesterol level seems to be an independent predictor of atherosclerosis. On the other hand, some individuals with monogenic familial hypertriglyceridemia (FHTG) and others with various familial abnormalities in lipoprotein lipase activity have very low levels of HDL cholesterol and are at no apparent increase in CAD risk. Some of this apparent paradox can be explained by study of the primary apoproteins carried in HDL, namely, apoproteins A-I and A-II. Many researchers have demonstrated a decrease in apo A-I in subjects with CAD. Some workers have also demonstrated decreased levels of apo A-II in these subjects, although others have found normal to slightly elevated apo A-II levels. Avogaro found decreased apo A-II levels in normolipidemic survivors of myocardial infarction, but normal levels in lipid-matched individuals with lipid phenotypes IIa, IIb, and IV. Since HDL contains discrete subpopulations based on apoprotein composition, some containing apo A-I without apo A-II and others with both apo A-I and A-II, changes in the apo A-I/A-II ratio might suggest alterations in the distribution of HDL subpopulations. Some workers found no overall change in the apo A-I/A-II ratio in CAD. Avogaro did note that the A-I/A-II ratio was decreased in individuals with lipoprotein phenotype IIB, but the ratio was normal in normolipidemic groups and in individuals with phenotypes IIA and IV when matched for lipid levels to control groups without CAD. DeBacker et al. reported a decreased apo A-I/A-II ratio in persons with CAD. These findings are compatible with a decreased level of the apo A-I particle. A decrease in the apo A-I/A-II ratio similar to that reported by DeBacker has been reported for familial combined hyperlipidemia and appears to be related to decreased levels of HDL. Apo A-I and A-II levels are both normal in FHTG, and are associated with a marked decrease in HDL cholesterol, but persons with FHTG do not seem to have increased risk for CAD.

The variation in methodology used to measure apoproteins A-I, A-II, and B might be expected to affect the results seen. Some assays were performed on whole plasma and others on lipoprotein fractions; some were measured by radioimmunoassay, others by radial immunodiffusion, and others by radioimmunoassay. In spite of this variation in methods, there was consistency among studies in the higher apo B and lower apo A-I seen in the patients as compared to the controls.

Other lipoprotein apoproteins may be related to the development of atherosclerosis. Avogaro et al. reported that apo D, a component of HDL, was decreased in normolipidemic survivors of myocardial infarction, while it was normal in those who were hyperlipidemic. Also, Wiklund et al. reported normal apo D levels in myocardial infarction survivors.

Future Questions

The case control studies examined here have demonstrated associations between coronary artery disease and lipoprotein apoprotein levels. These results often indicated that the apoproteins might be better indicators of risk for CAD than lipoprotein lipids. Only one small prospective cohort study has been performed. To determine the relative merit of each variable, prospective studies of a random population or selected populations of individuals at increased risk should be performed and evaluated by multivariate analyses.

It seems likely that there is an overlap of the subsets of individuals with hyper-B-apoproteinemia who have FCHL and those who have hyperapobetalipoproteinemia. Understanding of the nature and degree of overlap must await detailed studies of families of individuals selected for the presence of early CAD.

Heterogeneity of LDL particles has been reported by several groups. It is unknown how this heterogeneity is related to elevated plasma apo B levels,
but preliminary data suggest that heterogeneity of LDL is highly prevalent in hyperapobetalipoproteinemia and familial combined hyperlipidemia. Further studies are needed to establish this relationship. It remains to be determined whether this heterogeneity is due to the presence of discrete apoprotein families.

It is also not known whether the lipoprotein apoproteins are better predictors of atherosclerosis than are LDL and HDL cholesterol levels. Perhaps the association between specific apoproteins and atherosclerosis is related to particular characteristics of the lipoprotein subspecies involved. Also, in some situations a decrease in both apo A-I and A-II might reflect a reduction in total HDL, while in others a decrease in the apo A-I/A-II ratio may reflect a redistribution of HDL species without an absolute reduction in HDL mass.

It has been suggested that consideration of several lipoprotein apoproteins and lipids simultaneously might improve the prediction of CAD risk and peripheral vascular disease risk. The role of apoproteins D and E, and the Lp(a) lipoprotein in relation to apo B and apo A-I and A-II and their interaction in the genesis of atherosclerosis is as yet unknown.

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