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High-density-lipoprotein cholesterol and atherosclerosis

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An inverse relation between high-density-lipoprotein cholesterol (HDL-C) and the risk of coronary heart disease (CHD) was first reported in the 1950s. However, only since the report by Miller and Miller[1] in 1975 and a number of confirmatory epidemiologic studies in 1976 and 1977 did intensive research into the role of HDL in atherogenesis begin. Subsequently, numerous large-scale epidemiologic studies have continued to confirm the inverse relation.[2] In many instances the plasma HDL-C level was found to be a better predictor of CHD risk than either the total cholesterol level or the low-density-lipoprotein cholesterol (LDL-C) level. However, despite research into the biochemical, metabolic, epidemiologic and genetic features of HDL, a definitive causal relation to atherogenesis remains to be established.

On the one hand, the consistent inverse trend continues to provide the driving force to elucidate the pathogenetic link between HDL metabolism and atherogenesis. On the other hand, the complexity of its metabolism and the interactions of HDL with tissues so far preclude a clear-cut mechanism of causality. Many questions remain unanswered.

What are the mechanisms of cardioprotection of HDL?

Much progress has been made in our understanding of HDL metabolism. A low plasma HDL-C level seems to be an important risk factor for CHD in the general population. Likewise, a high level may confer cardioprotection. On the basis of data from a number of prospective studies[2] the risk of CHD increased by 2% to 3% for each decrease of 0.025 mmol/L in the HDL-C level. When the level was greater than 1.2 mmol/L in men and 1.45 mmol/L in women, the relative risk of CHD was less than 1.0.[3] Findings from animal studies have substantiated the protective effect of HDL-C. Badimon and associates[4] infused plasma HDL into rabbits given a high-cholesterol diet and observed a significant reduction in the occurrence of atherosclerotic plaques. Rubin and collaborators[5] made similar observations in transgenic mice overexpressing human apo A-I with elevated levels of HDL-C.

The role of HDL in reverse cholesterol transport — namely, its return of cholesterol from the peripheral tissues to the liver for catabolism — is well accepted.[6] The hypothesis that reverse cholesterol transport is the principal cardioprotective mechanism continues to receive much attention. However, HDL particles may have other antiatherogenic properties, such as an antioxidant effect and the ability to reduce LDL uptake by epithelial cells, prevent LDL aggregates from forming, counteract the platelet-activating effect of LDL, increase the solubility of cholesterol in bile and promote fibrinolysis. The relative contributions of each of these putative mechanisms remains to be established.

Are all HDL particles equally antiatherogenic?

HDL comprises a heterogeneous group of lipoprotein particles. The ability of individual subfractions of HDL to affect cholesterol efflux from a variety of cell types has been studied extensively. Conventionally, HDL has been subfractionated by ultracentrifugation into HDL_2 and HDL_3. It has been reported that HDL_2 may be the antiatherogenic fraction,[7] but other reports have yielded conflicting results.[8] More recently, HDL has been subfractionated by immunoaffinity chromatography into LpA-I (HDL containing only apolipoprotein [apo] A-I) and LpA-I/A-II (HDL containing both apo A-I and A-II).[9] Recent studies have suggested that the LpA-I subfraction is antiatherogenic. Furthermore, clinical studies have indicated that the level of apo A-I, not apo A-II, is decreased in patients with CHD.[10] This finding was confirmed by Puchois and colleagues:[11] in their study men with normolipidemic levels who had angiographically proven CHD had significantly lower levels of HDL and LpA-I, but not of LpA-I/A-II, than those who had no CHD. Turnover studies have shown that LpA-I and LpA-I/A-II are metabolically distinct.[12] If proven by

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large-scale prospective studies, this method of fractionation may be more informative than simple HDL-C determination in assessing an individual's risk of CHD.

What do we learn from genetics?

A number of kindreds have been reported to have genetically determined HDL deficiency caused by gene defects affecting apolipoproteins and enzymes in HDL metabolism.[13] Despite severe HDL deficiencies the risk of premature CHD was highly heterogeneous. Among the limited number of mutations reported to date, individuals who are unable to synthesize apo A-I (a major structural protein of the HDL particle), and hence unable to produce normal HDL, are more prone than others to premature CHD. This is further confirmed by a recent study in which a large Canadian kindred presented with heritable severe HDL deficiency that was caused by a premature termination of coding of the gene for apo A-I at the propeptide segment.[14] The affected homozygotes (six identified so far) were unable to synthesize any mature apo A-I. Three affected female members suffered premature CHD in their 30s.

That people with severe defects in apo A-I synthesis are prone to CHD lends credence to the putative direct antiatherogenic properties of HDL. However, it does not explain how certain kindreds with severe HDL deficiencies are spared from premature CHD. It also offers little insight into the antiatherogenic subpopulation of HDL. A recent clinical study showed that patients with CHD and a moderately decreased plasma HDL-C level tended to have increased catabolism of their HDL and apo A-I.[15] These findings lead to the hypothesis that a small loss of HDL particles (presumably a larger proportion of the more antiatherogenic subfraction) results in an amplified loss of cardioprotective function.

To complicate the issue further, all states of hypercatabolism of HDL are not equally proatherogenic. In patients with Tangier disease the observed severe HDL-C deficiency is caused by exaggerated catabolism of apo A-I by the reticuloendothelial tissues.[16] Similarly, the very low HDL-C concentration seen in patients with lipoprotein lipase deficiency is a direct consequence of abnormal postprandial handling of triglyceride-rich particles. Neither of these two conditions predisposes the affected person to premature CHD.

Low HDL-C levels — What do we do?

In the revised clinical practice guideline developed by the Adult Treatment Panel of the National Cholesterol Education Program[17] LDL continued to be considered the causative atherogenic lipoprotein. However, one important new development pertains to including HDL-C in the management strategy. A low plasma HDL-C level (less than 0.9 mmol/L) is considered to be a risk factor for CHD and a high level (greater than 1.6 mmol/L) a protective factor. Determination of the HDL-C level along with the total cholesterol level is recommended for initial screening among adults. Although a low HDL-C level by itself is not an indication for drug therapy, the level should be included in deciding when to start drug therapy and which drug to prescribe. Lipid-lowering agents with the best HDL-raising effect should always be used first. Data on the long-term benefit of drug therapy for isolated low HDL-C levels are still lacking. Raising the HDL-C level as a primary goal of therapy should still be limited to hygienic measures, including weight reduction, exercise and cessation of cigarette smoking.

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