Carotid Intima-Media Thickness in Familial Combined Hyperlipidemia and LDL Size

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In the article by Liu et al, as part of the European Multicenter Study on Familial Dyslipidemia (EUFAM), 1 148 asymptomatic familial combined hyperlipidemia members from 38 Finnish families were investigated for low-density lipoprotein (LDL) particle size, LDL susceptibility to oxidation, and the association of these LDL properties with carotid intima-media thickness (IMT) determined by ultrasound and B-mode scanning of 28 sites involving the common carotid artery, carotid bulb, and internal carotid artery. The authors found a statistically significant inverse relationship between LDL size (but not with LDL oxidation) and IMT. Using several multivariate analyses, the most rigorous also showed a correlation of IMT with pulse pressure and gender, but not with many of the other customary vascular risk factors such as hypertension, smoking, and total cholesterol.

This study is important in showing a potentially critical role for small, dense LDL particles in IMT expansion, a prelude to overt atherosclerosis. However, the precise role of small, dense LDL particles in this process still remains uncertain because no consensus exists. Some studies show no relationship of LDL size to atherogenesis, 2–4 while others show a strong correlation. This association is evident in the following: (1) subjects with the so-called metabolic syndrome or "syndrome X," a complex disorder including diabetes mellitus or insulin resistance plus hypercholesterolemia and hypertriglyceridemia; 5 (2) when more accurate separation of small LDL is undertaken (22.5 to 23.5 nm); and (3) in longitudinal follow-up of asymptomatic subjects who subsequently develop ischemic heart disease. 6 Persuasive support for the role of small, dense LDL in atherogenesis is, however, further suggested by studies showing them to be the particles that readily enter the subendothelial space of arteries 7 and that readily enter the subendothelial space of arteries 8 and bind there to proteoglycans, 9 which increases their residence time in this space, thereby increasing their susceptibility to oxidation by macrophages. 10

A most dramatically beneficial treatment for symptomatic coronary artery disease (CAD) to prevent recurrence of CAD and strokes is the use of statin drugs, 11 but the benefits are not associated with a selective reduction in small, dense LDL particles. 12 However, the Familial Atherosclerosis Treatment Study did show a strong relationship between a reduction in small, dense LDL particles and improved coronary stenosis, but these subjects were treated with either nicotinic acid plus cholestyramine or lovastatin plus cholestyramine. 13 Despite the results of these studies, because of the uncertainty of the small, dense LDL particles’ role in atherogenesis, the resolution of this question may likely come from drugs being developed that will reduce small, dense LDL formation by inhibiting cholesterol-ester transfer protein or microsomal triglyceride transfer protein. 12 Thus, while it is tempting to be reductionistic by simply implicating the small, dense LDL in atherogenesis, studies are needed that reproducibly and reversibly alter small, dense LDL concentrations to prove this assumption.

Oxidation of LDL is recognized to be a critical early step in atherogenesis, 14 and to this end various investigators have found a correlation between in vitro oxidizability of LDL and atherosclerosis, a presumed reflection of the in vivo susceptibility to oxidation. 15,16 On the other hand, others have found the exact opposite. Thus, the incubation of LDL with the pro-oxidant copper, and the production of conjugated dienes from polyunsaturated fatty acyl chains, do present technical problems (as the authors of the article note) that may indicate the need for a more reliable reagent to simulate the in vivo conditions. 17

Ultrasound and B-mode analyses of the carotid arteries for estimating IMT have advanced dramatically over the past decade, and their ready availability and relative low cost make them a desirable tools for monitoring IMT and progression. 18 However, MRI has distinct advantages over duplex scanning in assessing carotid atherosclerotic lesions because it can more precisely resolve the various constituents of plaques such as lipid, cells, connective tissue elements, calcification, extracellular matrix, and thrombus. 19 Because of this greater precision, future prospective studies proposing to analyze the dimensions and composition of the atheroma should consider MRI analyses. 20

References

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