Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study.


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BACKGROUND: Case-control studies have reported that patients with ischemic heart disease (IHD) have a higher proportion of small, dense LDL particles than do healthy control subjects. The extent to which the risk attributed to small LDL particles may be independent of concomitant variations in plasma lipoprotein-lipid concentrations remains to be clearly determined, however, particularly through prospective studies. METHODS AND RESULTS: Baseline characteristics were obtained in 2103 men initially free of IHD, among whom 114 developed IHD during a 5-year follow-up period. These 114 case patients were matched with healthy control subjects for age, body mass index, smoking habits, and alcohol intake. LDL peak particle diameter (PPD) was measured a posteriori in 103 case-control pairs by nondenaturing gradient gel electrophoresis of whole plasma. Conditional logistic regression analysis of the case-control status revealed that men in the first tertile of the control LDL-PPD distribution (LDL-PPD ≤ 25.64 nm) had a 3.6-fold increase in the risk of IHD (95% CI, 1.5 to 8.8) compared with those in the third tertile (LDL-PPD > 26.05 nm). Statistical adjustment for concomitant variations in LDL cholesterol, triglycerides, HDL cholesterol, and apolipoprotein B concentrations had virtually no impact on the relationship between small LDL particles and the risk of IHD.

CONCLUSIONS: These results represent the first prospective evidence suggesting that the presence of small, dense LDL particles may be associated with an increased risk of subsequently developing IHD in men. Results also suggest that the risk attributed to small LDL particles may be partly independent of the concomitant variation in plasma lipoprotein-lipid concentrations.

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Lipoprotein subclasses in the Monitored Atherosclerosis Regression Study (MARS). Treatment effects and relation to coronary angiographic progression.

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Accumulating evidence suggests that triglyceride-rich lipoproteins contribute to coronary artery disease. Using data from the Monitored Atherosclerosis Regression Study, an angiographic trial of middle-aged men and women randomized to lovastatin or placebo, we investigated relationships between lipoprotein subclasses and progression of coronary artery atherosclerosis. Coronary artery lesion progression was determined by quantitative coronary angiography in low-grade (< 50% diameter stenosis), high-grade (> or = 50% diameter stenosis), and all coronary artery lesions in 220 baseline/2-year angiogram pairs. Analytical ultracentrifugation was used to measure lipoprotein masses that were statistically evaluated for treatment group differences and relationships to progression of coronary artery atherosclerosis. All low density lipoprotein (LDL), intermediate density lipoprotein (IDL), and very low density lipoprotein (VLDL) masses were significantly lowered and all high density lipoprotein (HDL) masses were significantly raised with lovastatin therapy. The mass of smallest LDL (Svedberg flotation rate [Sf] 0 to 3), IDL (Sf 12 to 20), all VLDL subclasses (Sf 20 to 60, Sf 60 to 100, and Sf 100 to 400), and peak LDL flotation rate were significantly related to the progression of coronary artery lesions, specifically low-grade lesions. Greater baseline levels of HDL3, were related to a lower likelihood of coronary artery lesion progression. In multivariate analyses, small VLDL (Sf 20 to 60) and HDL3 mass were the most important correlates of coronary artery lesion progression. These results provide further evidence for the importance of triglyceride-rich lipoproteins in the progression of coronary artery disease. In addition, these results present new evidence for the possible protective role of HDL3 in the progression of coronary artery lesions. More specific information on coronary artery lesion progression may be obtained through the study of specific apolipoprotein B-containing lipoproteins.

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Particle Size: The Key To The Atherogenic Lipoprotein?

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Using different analytical methods, up to 12 low-density lipoprotein (LDL) subfractions can be separated. LDL particle size decreases with increasing density. Smaller, denser LDL particles seem more atherogenic than the larger, lighter particles, based on the experimental findings that smaller LDL particles are more susceptible for oxidation in vitro, have lower binding affinity for the LDL-receptors and lower catabolic rate, have a higher concentration of polyunsaturated fatty acids, and potentially interact more easily with proteoglycans of the arterial wall. Clinical studies have shown that a smaller LDL-subfraction profile is associated with an increased risk of heart disease, even when total cholesterol level is only slightly raised. There is a strong inverse association between LDL particle size and triglyceride concentrations. Although LDL particle size is genetically determined, its phenotypic expression may also be affected by environmental factors such as drugs, diet, obesity, exercise or disease. Factors that shift the LDL-subfractions profile towards larger particles may reduce the risk of heart disease.

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Identification and characteristic of LDL-subfractions in human plasma.

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Density gradient ultracentrifugation and high resolution polyacrylamide gel electrophoresis (Lipoprint LDL-system) were used to examine the discrete LDL subfraction patterns in normal and hyperlipidemic patients. Two new programs for LDL and VLDL subfractions were elaborated and a new method of evaluation for cholesterol content in LDL-subfractions, based on area distribution ratio of densitograms without density gradient ultracentrifugation, was created. The predominance of cholesterol and triglycerides in dense LDL3-subclass (d-1,048-1,063 g/ml) under hypercholesterolemia and hypertriglyceridemia was found. Lipoprint LDL-electrophoresis method was developed for the characteristic of lipemic state of organism and detection and quantitation of plasma LDL subfractions.

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