Metabolic studies of lipoproteins have yielded important insights into regulation of energy distribution as well as providing fundamental understanding of cardiovascular risk properties of different lipoproteins. Although many factors on the molecular level have the potential to impact metabolic regulation of lipids, metabolic studies provide valuable information from a comprehensive regulatory viewpoint. With increasing emphasis on lipoprotein subfractions and their roles in promoting or protecting from cardiovascular risk, the focus of metabolic studies is largely moving toward more detailed understanding of lipoprotein subclass and individual apolipoprotein properties.

The atherogenic and antiatherogenic roles of LDL and HDL cholesterol, respectively, are well established and, by now, part of the general public knowledge. However, hereditary diseases of lipoprotein metabolism with dramatically different LDL and/or HDL cholesterol levels offer great promise to further investigate this complex system, and we have already gained considerable insight from such studies. Thus, it is well known that some hereditary conditions result in phenotypes with unusual LDL and HDL compositions. Thus, carriers of apoA-I Milano appear protected from cardiovascular disease in spite of low HDL cholesterol levels.1,2 In another hereditary condition, lecithin:cholesterol acyltransferase (LCAT) deficiency, HDL metabolism is severely affected, and carriers of this deficiency have low levels of both HDL and LDL cholesterol with the accumulation of an aberrant lipoprotein, Lp-X.3,4 However, in spite of low HDL cholesterol levels, cardiovascular disease is not common among LCAT-deficient subjects.5,6 LCAT is critical for esterification of cholesterol, and in the absence of this enzyme HDL maturation is affected, resulting in small discoidal HDL particles which are thought to be deficient in promoting reverse cholesterol transport.7 On the other hand, LDL particles are also affected by the deficiency in cholesterol esterification and have higher relative amounts of phospholipids, triglyceride, and cholesterol.8,9

The physicochemical changes in lipoprotein properties observed in LCAT deficiency are likely to be associated with significant metabolic aberrations. Thus, the relative lack of cholesteryl esters in LDL could result in an LDL fraction with reduced atherogenicity, which might contribute to the apparent lack of CAD in these patients. The relative triglyceride enrichment of LDL under these conditions might further make LDL a better substrate for lipase activity, which could contribute to a reduction in LDL plasma circulation time. In a study of 2 LCAT-deficient patients and 17 normal subjects, Nishiwaki et al report on the metabolic basis for the complex changes in LDL properties in LCAT-deficiency in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology.10 As expected, the LCAT-deficient subjects had very low HDL cholesterol levels and also lower apoA-I, apoB, and LDL cholesterol levels than the normal controls. It has been well established in previous studies based on treatment with hypolipidemic agents that net LDL clearance is affected by both LDL receptor activity and LDL particle properties.11–13

In LCAT deficiency, these factors, LDL receptor activity and LDL properties, are likely to differ between patients and normals. Thus, it would be expected that (1) metabolism of LCAT-LDL (L-LDL) and normal LDL (N-LDL) metabolism would differ in the same subject, irrespective of being LCAT deficient or normal, and (2) that clearance of either N-LDL or L-LDL could differ between normals and LCAT-deficient patients. In recognizing these possibilities, the authors used several approaches in their metabolic studies. First, they directly compared metabolic properties of LDL from normals and LCAT-deficient subjects in the same subjects, using different radiotracers for the 2 LDL preparations. To control for a relatively low density of LDL in LCAT-deficiency, the N-LDL recovered represented a comparable density spectrum (1.03 to 1.05 g/mL). The results from these studies revealed that L-LDL had a faster clearance than N-LDL in both LCAT-deficient patients and in controls. Further, when comparing clearance of the tracers across patient groups, both N-LDL and L-LDL were catabolized faster among the LCAT-deficient patients.

In conclusion, these studies suggest an upregulation of LDL receptors in LCAT-deficiency as well as a change in LDL particle properties, resulting in faster clearance of LDL from LCAT-deficient subjects compared with LDL from normals. These results differ from changes induced by hypolipidemic agents, where upregulation of LDL receptor commonly result in the initial clearance of particle with higher receptor affinity, causing accumulation of particles with a lower affinity for the receptor.11–13 The changes observed in LCAT deficiency are consistent with a double effect on LDL clearance compared with normals—increased

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**Editorial**

**Lipoprotein Metabolism**

A Well-Tried Tool to Characterize Dyslipidemic Mechanisms

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particle clearance, perhaps attributable to triglyceride enrichment, and a simultaneous increase in LDL receptor activity, likely resulting from a relatively decreased uptake of cholesteryl ester by the liver (Figure).

In a second part of their study, Nishiwaki et al used stable isotope techniques for endogenous labeling, allowing an estimation of VLDL- and IDL apoB kinetics as well as LDL apoB kinetics. They report an unchanged VLDL or IDL apoB clearance but an increased VLDL apoB-production rate in parallel with a decrease in IDL apoB production in the patients. In the LCAT-deficient subjects, more of the VLDL was cleared directly and less converted to IDL and LDL compared with normals. Whether a faster clearance of VLDL can be explained by an upregulation of LDL receptors or is attributable to other mechanisms remains to be shown. However, there was no indication of an impaired conversion of VLDL to LDL in LCAT deficiency.

Altogether, the results by Nishiwaki et al show profound changes in the metabolism of apoB-containing lipoproteins in LCAT deficiency, and they provide a basis for conclusions regarding the lower net atherogenic potential of LDL in these subjects. However, whether these observations explain the apparent protection from cardiovascular disease in these patients, or whether other mechanisms, such as alternative pathways for reverse cholesterol transport are contributory, remain to be seen. Whether the present results on LDL metabolism can be extrapolated to all subjects with LCAT deficiency is less clear, as larger studies of LCAT deficient subjects have shown a wide interindividual variability in LDL cholesterol levels. Interestingly, studies on heterozygotes for LCAT deficiency have shown the presence of atherosclerosis, which might perhaps suggest that any sizeable presence of “N-LDL” may contribute to atherogenicity under heterozygous or partial LCAT deficient conditions. In conclusion, the present studies illustrate the ability to dissect complex metabolic changes using carefully designed tools, and they offer a mechanistically plausible explanation for the observed effects on metabolism of apoB-containing lipoproteins in LCAT deficiency.

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References


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