Lipoproteins in LCAT-Deficiency*

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Summary. Purified lipoproteins from 2 brothers and 1 unrelated male patient with lecithin-cholesterol-acyltransferase deficiency were investigated. All 3 patients exhibited the changes in properties of high-density-lipoproteins that have been described in familial lecithin-cholesterol-acyltransferase deficiency. In all 3 patients we also observed a low-density-lipoprotein indistinguishable from the LP-X protein characteristic of obstructive jaundice. Criteria of comparison were electrophoretic mobility, flotation behaviour, immunological properties, appearance in electron microscopy and lipid composition.

In 2 of the patients there was no sign of biliary obstruction (brothers G. M. and P. M.); it, therefore, is assumed that they suffer from the familial form of LCAT-deficiency, whereas the third patient (V. M.) exhibited signs of intrahepatic obstruction.

From this as well as from further comparative studies of patients with biliary obstruction it is concluded that there exists a primary and a secondary form of LCAT-deficiency, both of which may result in the same changes of lipoprotein patterns.

In the present study the disease was found to be characterized mainly by 1. two different abnormal lipoproteins, one of low density containing apoprotein C and albumin, and the other of high density containing apoprotein A, both of which demonstrate a disk-like appearance with a tendency to rouleaux formation, when examined by electron microscopy, and 2. by a protein with immunological properties of apoprotein A in fractions HDL₃ and ρ > 1.21 g/ml, that does not stain with lipid dyes.


Diese Veränderungen werden charakterisiert durch 2 verschiedene, abnorme Lipoproteine mit einer gesteigerten Tendenz zur rouleaux-Formation. Das eine wurde in der Fraktion der low density-Lipoproteine gefunden und enthielt Apoprotein C und Albumin, das andere in der Fraktion der high density-Lipoproteine und enthielt Apoprotein A. Ein weiteres Protein mit den immunologischen Eigenschaften von Apoprotein A, das nicht mit Lipidfärbungen anfärbbar war, fand sich in den Fraktionen HDL₃ und ρ > 1.21 g/ml.

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Introduction

The enzyme lecithin-cholesterol-acyltransferase (LCAT) is responsible for the transfer of acyl residues of fatty acids from lecithin to cholesterol, resulting in lysolecithin and cholestereoler (Glomset et al., 1966).

The main substrates of the enzyme are the $\alpha_1$-lipoproteins of subclasses HDL$_3$ and very high-density-lipoproteins (Fielding and Fielding, 1971).

Recently in Scandinavia there has been described a genetic disorder termed LCAT-deficiency, apparently caused by the lack of activity of this enzyme (Norum and Gjone, 1967; Hamnström et al., 1969; Norum et al., 1970).

Clinically the LCAT-deficiency is characterized by proteinuria, anaemia with target cells and by a typical opacity of the cornea. The disease is assumed to be inherited as an autosomal recessive.

Drastic changes were found in the distribution and properties of lipoproteins and lipids in the sera of patients suffering from this disorder (Torsvik, 1969, 1970; Norum et al., 1971; Forte et al., 1971). Patients exhibited hyperlipidaemia. The ratio of free cholesterol to esterified cholesterol was elevated, whereas $\alpha_2$-lipoprotein levels were reduced to about 25% of normal. Most characteristic, however, was the rouleaux-formation of high-density-lipoproteins as revealed by electron microscopy (Torsvik et al., 1970; Forte et al., 1971). Within the LDL (1.006—1.063 g/ml) fraction, particles of unusual size and electrophoretic mobility were observed. They had a high molecular weight and upon gel-electrophoresis remained at the application site.

Similar changes in lipoprotein distribution were described in patients with obstructive jaundice (Switzer, 1967; Seidel et al., 1969). Intra- as well as extra-hepatic cholestasis are characterized by the occurrence of the abnormal lipoprotein LP-X within the LDL-fraction (1.006—1.063 g/ml) of serum. This protein exhibits an extremely high content of phospholipids and cholesterol, and its protein moiety is composed of apoprotein C and albumin (Seidel et al., 1970). In agar-gel-electrophoresis it moves towards the cathode. Electron microscopic studies by Seidel (1970) and by Hamilton et al. (1971) revealed rouleaux-formation of the lipoprotein particles.

In this study we present our results concerning lipoprotein abnormalities in LCAT-deficiency as revealed by comparison of 3 patients, 1 with severe intra-hepatic obstruction, and 2 brothers probably suffering from a familial form of LCAT-deficiency.

Materials and Methods

Isolation of Lipoproteins. Lipoprotein fraction $q < 1.063$ g/ml, HDL$_2$ and HDL$_3$ were obtained by ultracentrifugation in a Beckman L2-50B centrifuge as described by Utermann (1971).

Fraction HDL$_2$ and HDL$_3$ were further purified by additional centrifugations at the appropriate densities. LDL$_2$-lipoproteins were obtained from the $q < 1.063$ g/ml fraction. This was extensively dialysed against a KBr/NaCl-solution of density 1.019 g/ml and centrifuged at this density in a 40.2 rotor for 24 hrs at 6°C.

The supernatant containing the VLDL and LDL$_1$-lipoproteins was discarded, the bottom fraction adjusted to density 1.063 g/ml and centrifuged under identical conditions.