Clinical Biochemistry 48 (2015) 472–475

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

A review on lecithin:cholesterol acyltransferase deficiency

Ramesh Saeedi, Min Li, Jiri Frohlich *

Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, Canada

ARTICLE INFO

Article history:
Received 17 June 2014
Received in revised form 19 August 2014
Accepted 20 August 2014
Available online 27 August 2014

Keywords:
LCAT deficiency
FED
FLD
Cholesterol
HDL

ABSTRACT

Lecithin cholesterol acyl transferase (LCAT) is a plasma enzyme which esterifies cholesterol, and plays a key role in the metabolism of high-density lipoprotein cholesterol (HDL-C). Genetic disorders of LCAT are associated with lipoprotein abnormalities including low levels of HDL-C and presence of lipoprotein X, and clinical features mainly corneal opacities, changes in erythrocyte morphology and renal failure. Recombinant LCAT is being developed for the treatment of patients with LCAT deficiency.

Contents

Introduction

Lecithin:cholesterol acyltransferase (LCAT), first was identified by Glomset et al. in 1962 [1], is a lipoprotein-associated enzyme which plays a central role in the esterification of free cholesterol (FC), in the formation of mature high density-lipoprotein (HDL) particles, and in the intravascular stage of reverse cholesterol transport (RCT) [2–4]. In 1976 the case history of three sisters with LCAT deficiency was published [5]. To date, around 70 families, together accounting at least 60 isolated cases of partial or complete LCAT deficiency have been identified worldwide [6].

LCAT structure & function

Human LCAT is a glycoprotein of 67-kDa size consisting of 416 amino acids encoded by a gene on chromosome 16 (region 16q22) [2–4]. The human LCAT protein is synthesized mainly in the liver, with smaller amount in the testis and brain. It binds mainly to HDL particles with a smaller proportion binding to apolipoprotein (apo)B (apo B) containing lipoproteins [7]. The plasma LCAT level correlates with its activity. It is about 5 mg/L and varies a little by gender, smoking, age, and alimentary habits [8]. Its half-life is 4–5 days.

LCAT esterifies majority of the free cholesterol (FC) located at the surface of lipoprotein particles by catalyzing translocation of fatty acid moiety in sn-2 position of lecithin (phosphatidyl choline) to the free 3-OH group of cholesterol [9]. This reaction takes place mostly in the circulating newly formed HDL; however, LCAT activity is also detected in apo B100-containing lipoproteins [2–4]. The esterified cholesterol migrates to the core of the particle resulting in its increased size. Therefore, LCAT plays a major role in HDL maturation. LCAT maintains the

* Correspondence to: Clinical Trials Director, Healthy Heart Program, St. Paul's Hospital Professor, Pathology and Laboratory Medicine Department, University of British Columbia, St. Paul's Hospital, Rm 180-1081 Burrard Street, Vancouver, B.C. V6Z 1Y6, Canada.
E-mail addresses: rsaeedi@providencehealth.bc.ca (R. Saeedi), minli@providencehealth.bc.ca (M. Li), jifr@mail.ubc.ca (J. Frohlich).

http://dx.doi.org/10.1016/j.clinbiochem.2014.08.014
0009-9120/

unesterified cholesterol gradient between HDL particles and peripheral cells. The free cholesterol (FC) efflux occurs by a passive diffusion of FC between cellular membrane and acceptor and this mechanism is facilitated by ATP-binding cassette transporters (ABCs) and scavenger receptor type B-I (SR-BI). In the presence of LCAT, the net bi-direction of FC between cells and HDL particles is toward HDL. Thus, LCAT also plays a key role in RCT, the major mechanism by which HDL exerts antiatherosclerotic effects [10].

Apolipoprotein (apo) A-I (apo A-I) is the main activator of LCAT; however, it also can be activated by apo A-II, apo C-I, and apoE. Both binding and activation of LCAT on surface of HDL particles are crucial for FC esterification and accumulation of cholesteryl esters in the core of HDL particles [11].

In normal plasma, LCAT demonstrates two activities; alpha-LCAT activity, specific for alpha-migrating lipoproteins (HDL), and beta-LCAT activity, specific for beta-migrating lipoprotein on gel electrophoresis including very low density lipoprotein (VLDL), and LDL. These alpha- and beta-LCAT activities are two functional aspects of the same protein. While the beta form has a shorter half-life and is rapidly cleared by the kidney, alpha form has a slow turnover [3,9].

LCAT deficiency

LCAT deficiency is a rare autosomal recessive disease with prevalence below 1:1,000,000. More than 80 mutations in the LCAT gene have been identified [12]. Mutations in both alleles of LCAT gene may lead to two syndromes namely, familial LCAT deficiency (FLD), and fish eye disease (FED). The clinical manifestation and biochemical characteristics of these disorders are summarized in Table 1.

In general patients with the deficiency have several abnormalities of their serum lipoproteins including a decrease in the levels of HDL, apo A-I and apoA-II, decrease in LDL, increase in serum levels of FC and apo E, and accumulation of lipoprotein X (Lp-X) [11,13]. Lp-X is a large multilamellar phospholipid vesicle containing various apolipoproteins without a neutral lipid core. Lambert et al. [14] demonstrated that Lp-X-associated renal disease in a subset of LCAT knockout mice that were on atherogenic diet. These mice had Lp-X accumulation, proteinuria and glumerulosclerosis characterized by significant reductions in the vascular space, mesangial cells proliferation and sclerosis, and accumulation of lipid droplets and macrophages. The oil red-O staining reveals accumulation of free cholesterol in the glomeruli. These mice did not show any ocular abnormalities. Nishiwaki et al. [15] found that Lp-X catabolic rate in the LCAT-deficient patients is slower than controls in which this may explain the Lp-X accumulation in these patients. Also the same group found that LDL is decreased in LCAT deficient patients due to increased catabolism of LDL. The proposed mechanism for high LDL catabolism is due to a rapid catabolism of abnormal LDL and LDL-receptor upregulation.

Table 1
Biochemical and clinical characteristics of FED and FLD.

	FLD	FED
Clinical findings		
Corneal opacity	++	+
Anemia	+	−
Nephropathy	+	−
Routine laboratory		
Triglyceride	↑	→↑
Total cholesterol	↓	→
Low-density lipoprotein	↓	→
High-density lipoprotein	↓↓	↓↓
Very low-density lipoprotein	↓	→
Hemoglobin	↓	→
Proteinuria	+ (in most cases)	−
Special laboratory		
Unesterified cholesterol	↑	→
LCAT activity	Absent	↓
LCAT mass	↓	→↓
Renal biopsy	Abnormal (in most cases)	→
Cholesterol esterification rate	↓↓	→
Apolipoprotein A-I	↓↓	↓↓
Apolipoprotein A-II	↓	↓
Apolipoprotein E	↑	↑

The HDL level in LCAT deficient patients is decreased; also HDL particles are small and resemble newly synthesized HDL (immature HDL).

In FED (MIM#136120), characterized by a partial enzyme deficiency, there is a loss of alpha-LCAT activity while the beta-LCAT activity is preserved [9,16–18]. Here, LCAT does not esterify cholesterol in the HDL, but it esterifies cholesterol in VLDL and LDL. Individuals with FED have very low level of HDL, and corneal opacities.

FLD (MIM#245900) is characterized by complete lack of LCAT activity [9,16–18]. In affected individuals, LCAT is either absent or present but is inactive. It affects both the esterifications on HDL (alpha-LCAT activity) and LDL (beta-LCAT activity) [9,16–18]. There is very little CE in plasma; therefore, the unesterified cholesterol accumulates in all plasma lipoproteins. The patients may present with HDL-C deficiency, corneal opacification, hemolytic anemia, hypertension, hypertriglyceridemia, and proteinuria frequently progressing to end stage renal disease (ESRD). Prognosis of subjects with FLD depends on their renal function. The diagnosis of FLD is mainly based on clinical manifestation in combination with histological finding from kidney biopsy (glomerulopathy evolving toward sclerosis with lipid deposition). Renal involvement is a major cause of morbidity and mortality in FLD patients [17,18]. It starts as proteinuria in childhood progressing to renal insufficiency by the fourth decade [17,18].

The renal disease is characterized by deposition of Lp-X particles mainly in the glomeruli [12,13,17]. This accumulation is suggested to be the main mechanism behind the development of renal disease. Light microscopic examination in the early stage reveals mild mesangium enlargement and thickening of glomerular basement membrane (GBM). Deposition of foamy lipids is observed in the thickened GBM. Similar findings are also observed in the interstitial blood vessel wall. Renal tubules may become atrophic. The electron microscopic findings are the most characteristic with lipid deposition in GBM, in the extracellular matrix, in the Bowman's capsule, and in the vascular endothelium. The renal disease in these patients may progress to EDRD requiring dialysis therapy or renal transplant.

Corneal opacification is a gradual process which usually starts early in life and often represents the initial symptom of this disease [19]. Some patients may need corneal transplantation. Analysis of cornea of these patients during corneal transplantation revealed that cornea contains large depositions of FC and phospholipid.

Anemia in these patients is a hemolytic normochromic normocytic anemia with a reduction of hemoglobin level to about 10 g/dl. It is caused by FC and phosphatidylcholine deposition in erythrocyte membrane-induced shortening of the lifespan of erythrocytes [12]. In bone marrow of these patients foam cells and sea-blue histiocytes are found [20].

The differential diagnosis of FLD and FED in carriers (only one allele is affected) is based on the measurement of the ability of their plasma to esterify cholesterol (alpha-LCAT activity) [14].

LCAT deficiency and atherosclerosis

HDL cholesterol level is believed to inversely correlate with the progression of atherosclerosis (AS) [6]. Thus, theoretically in patients with LCAT deficiency a higher rate of AS would be expected. Even though in some patients with FLD AS has been reported (with carotid, aortic, and femoral atherosclerosis), no premature coronary heart disease has been reported in this setting [21].

Patients with LCAT deficiency have low levels of HDL, but the association between LCAT deficiency and AS is not well established [6,21]. While some studies show association between LCAT levels and AS