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REVIEW

Lipoprotein-X fifty years after its original discovery☆

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Abstract *Aims:* To review the formation, catabolism, and the possible atherogenic properties of Lp-X.
Data Synthesis: The conversion of cholesterol to bile acids is regulated by several mechanisms including cholesterol 7 alpha hydroxylase, fibroblast growth factor 19, and farnesoid X receptors. During cholestasis these mechanisms are altered and there is an accumulation of bile acids and cholesterol in plasma. The hypercholesterolemia observed in cholestasis is due to the presence of an anomalous lipoprotein called lipoprotein-X (Lp-X).

Lp-X is a lipoprotein rich in phospholipid and free cholesterol present in plasma of patients with cholestasis and, with some variations, in patients with lecithin-cholesterol-acyl-transferase deficiency (LCAT), and after lipid infusion.

Lp-X is formed from a bile lipoprotein moving to the blood vessels where it incorporates small quantities of triglycerides, apo-C and esterified cholesterol and becomes a “mature” Lp-X. The activity of the phosphatidilcholine canalicular transporter Mdr2 P-glycoprotein (homologous to the human ABCB4) is essential for LpX appearance, since its suppression abolishes Lp-X formation. However, the concentration of Lp-X in plasma is determined also by the degree of the cholestasis, the residual liver function, and the LCAT deficiency. The Lp-X catabolism seems to be mediated by the reticuloendothelial system and possibly the kidney.
Conclusions: Lp-X might be considered a defense mechanism against the toxic effect of free cholesterol in cholestasis. The frequency of cardiovascular events in patients affected by primary biliary cholangitis, in whom the Lp-X is present in high concentration, are not increased.

Further studies could now clarify the remaining open questions on the role of Lp-X in the dyslipidemia of cholestasis.

Introduction

In cholestasis the impaired bile flow results in an accumulation of bile acids and other metabolites in the liver and in the systemic circulation. Cholestasis is responsible of liver injury and inflammation and of biliary epithelium damage. Chronic cholestasis may lead to fibrosis, cirrhosis, and eventually to hepato- and cholangio-cellular carcinomas.

Abbreviations: Lp-X, lipoprotein-X; LCAT, lecithin-cholesterol-acyl-transferase; Lp(a), lipoprotein (a).

☆ This work is dedicated to Dietrich Seidel on his 80th birthday (May 2, 2018), fifty years after the first paper on Lp-X (1969–1970) was published.

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Bile acids, phospholipids, and cholesterol are the most abundant organic compounds of the bile. These molecules are organized in micelles thus increasing cholesterol solubility and reducing bile acids toxicity. Several alterations in their metabolic pathways are affecting these compounds during cholestasis [1].

Hypercholesterolemia, with a relative increase of free cholesterol, is one of the earliest and most peculiar metabolic alteration in cholestasis. Conversion of cholesterol to bile acids is the major mechanism by which cholesterol is eliminated from the body and represents a key step in the maintenance of cholesterol homeostasis. Hydroxylation at 7 alpha position is the first and rate limiting step in this metabolic pathway and it is largely dependent on a feed-back mechanism exerted by bile acids recirculating to the liver. This mechanism is demonstrated both in experimental models and in humans. In patients with extra-hepatic cholestasis cholesterol hydroxylation rate is lower than in controls and this reduction is proportional to the severity of cholestasis. The synthetic rate is normalized after resolution of biliary obstruction [2].

In the primary biliary cholangitis (PBC) there is a persistent and severe intra-hepatic cholestasis with associated hypercholesterolemia. In this disease there is also a deficient feedback regulation of retained bile acids on cholesterol 7 alpha hydroxylase [3].

More recently other molecular regulators of the bile acid homeostasis were described. In response to uptake of luminal bile acids the small intestine produces the Fibroblast Growth Factor 19 (FGF19) that in the liver binds to FGF receptor-4 resulting in a down-regulation of cytochrome P7A1 and a reduced bile acid synthesis, thus protecting the liver from bile acid toxicity [4]. In PBC the bile acid synthesis is primarily controlled by circulating FGF19, whose concentration is proportionally increased in response to the severity of cholestasis [5,6].

Moreover, in the liver and in the intestine the nuclear hormone receptors, Farnesoid X Receptors (FXRs), by regulating several genes, are important modulators of bile acid, cholesterol, triglyceride, and lipoprotein metabolism including lipoprotein(a) [7]. By binding to the FXRs bile acids repress the expression of the gene encoding for cholesterol 7 alpha-hydroxylase, the rate-limiting step for bile acid synthesis, thus protecting the liver against the toxic accumulation of bile acids [8].

During cholestasis both composition and metabolism of plasma lipoproteins are altered. The most frequent alteration being the hypercholesterolemia due to the presence of an anomalous lipoprotein called lipoprotein-X (Lp-X). Between 1969 and 1970 two seminal studies described a lipoprotein rich in phospholipid and free cholesterol in plasma of patients with cholestasis. That lipoprotein was called Lp-X to underline its mysterious origin [9,10]. As the 50th anniversary of the discovery of Lp-X approaches, it seems appropriate to commemorate the date by reviewing the findings on this particular lipoprotein and its clinical and physiopathological implications. Studies focusing on this lipoprotein enhanced our understanding of the rise of plasma cholesterol and the metabolism of phospholipid, cholesterol, and bile acid in cholestatic patients [11,12]. Since that time, PubMed has registered 339 papers focusing on Lp-X, 63 since 2001 alone. This short review seeks to summarize the data that emerged about this abnormal lipoprotein and to examine some of the open questions that still remain.

Characteristics of Lp-X and clinical significance

Lp-X is isolated by ultracentrifugation in the 1.019–1.063 g/ml density range as the normal LDL. Three fractions of Lp-X with different density and protein contents were described [13]. At the electronic microscope, Lp-X appears as flattened discoidal vesicles, 50–70 nm in diameter, often forming rouleaux [14,15] (Fig. 1). The composition of Lp-X is quite different from that of normal plasma lipoproteins; it contains phospholipids (66%), free cholesterol (22%), and albumin as protein moiety (6%) [9,10]. Small quantities of triglycerides, esterified cholesterol, and apo-C and E were also identified in Lp-X [16]. Using immunoelectrophoresis and other techniques a physical association between Lp-X and alkaline phosphatase (and other enzymes derived from hepatocyte membrane) of high relative molecular mass were demonstrated in some patients with cholestasis, particularly in cholestasis due to liver malignancy [17,18]. The plasma ratio of albumin to biliary salts is important to maintain the Lp-X's structural integrity [19].

Lp-X is present in plasma of patients affected by extra- and intra-hepatic cholestasis (due to bile duct obstruction, primary biliary cholangitis, primary sclerosing cholangitis, or cholestatic hepatitis) and, with some variations, by rare lecithin-cholesterol-acyl-transferase (LCAT) deficiency, and after lipid infusion (e.g. Intralipid). Since Lp-X does not contain apo-AI, the LCAT activator, it is not a substrate for this enzyme [20] and rapidly disappears from plasma when the cause of cholestasis is removed.

Differently from normal lipoproteins, Lp-X has a peculiar cathode mobility in agar gel electrophoresis, so that it

Figure 1 Electron micrograph of the Lp-X particles isolated from cholestatic plasma.

is relatively easy to identify its presence in patients with cholestasis (Lp-X test) [21,22]. When histologic features are used for confirmation, a positive Lp-X test shows a higher than 95% concordance for the presence of cholestasis [23]. Although the presence of Lp-X is not useful to discriminate between intra- and extra-hepatic cholestasis, the test was used in the past to help diagnosing this condition before the most recent imaging techniques became popular. High concentrations of Lp-X may produce plasma hyperviscosity or planar xanthomata, which rapidly resolve when the cause of cholestasis is removed [24]. The hyperviscosity syndrome, a possible cause of hyponatremia, may be treated with lipoprotein apheresis or plasma exchange [25].

On the basis of some experimental data it is unlikely that Lp-X could produce an atherosclerotic damage.

In fact, the diameter of the atherogenic LDL is 18–25 nm, while Lp-X is 3 times larger (50–70 nm diameter) and quite similar to the VLDL size (30–80 nm diameter). VLDL particles are too large to pass through the arterial endothelium and are practically excluded from entering the arterial wall [26]. Moreover, some Authors hypothesized that the Lp-X particle has anti-atherogenic properties since it reduces LDL oxidation and preserves endothelial homeostasis [27,28].

The clinical studies that examined the frequency of cardiovascular events in patients affected by primary biliary cholangitis (used as hallmark for the hypercholesterolemia of cholestasis) concluded that cardiovascular risk is not increased in these patients. While two of these studies [29,30] reported that cardiovascular events were significantly reduced with respect to control subjects, another argued that there were no differences in the two populations [31]. A recent study concluded that the hypercholesterolemia of the primary biliary cholangitis is not associated by itself with subclinical atherosclerosis as evidenced by ultrasound imaging of carotid arteries [32]. However, in the same paper it is reported that in these patients an increased risk of subclinical atherosclerosis is present when hypercholesterolemia is associated with hypertension and old age. Even the appearance of planar xanthomata in cholestasis does not seem to be correlated to the frequency of ischemic heart disease [28,33].

Since in the absence of liver failure plasma cholesterol concentrations are increased in cholestasis, the cholesterol present in Lp-X needs to be distinguished from that of normal LDL. The distinction is important in order to establish the real cardiovascular risk and thus to enable clinicians to prescribe appropriate interventions. Quantifying plasma apo-B, which is present in LDL but not in Lp-X, is important to make this distinction.

Formation and catabolism of Lp-X

Lp-X appears in the plasma of dogs starting 24–30 h after common bile duct ligation [34]. Lp-X can be formed in vitro by combining bile (containing the bile lipoprotein) with albumin or serum [19]. The Lp-X-like material that is formed in this way has physicochemical characteristics (including density range and behavior using precipitation techniques) very similar or identical to Lp-X isolated from cholestatic serum. It would seem then that Lp-X is formed by a bile lipoprotein moving to the blood vessels where it incorporates small quantities of triglycerides, apo-C and esterified cholesterol and becomes a "mature" Lp-X [19] (Fig. 2).

To confirm this observation, Felker et al. demonstrated that the discoidal vesicles present in the liver perfusate of rats with biliary ligation are similar to the Lp-X present in plasma. Using the same experimental model, electron micrographs have uncovered the presence of structures similar to Lp-X in the biliary canaliculi and near cytoplasmic vacuoli. Since these structures were never observed in the smooth endoplasmic reticulum nor in the Golgi apparatus of the liver cells, this suggests that Lp-X formation takes place in an extracellular compartment, probably within the biliary canaliculi [35].

The phosphatidilcholine canalicular transporter Mdr2 P-glycoprotein (homologous to the human ABCB4) is localized in the canalicular membrane of the hepatocyte which translocates phosphatidylcholine from the inner to the outer leaflet of the cell membrane, thereby making it available for secretion into canalicular lumen. The action of Mdr2 P-glycoprotein and bile acids secretion leads to the formation of biliary vesicles at the canalicular membrane [36]. During cholestasis the biliary vesicles formed near the canalicular part of the hepatocyte membrane seem then to be transported through the cytoplasm (transcytosed) to the sinusoidal membrane and released into the plasma. Mdr2 P-glycoprotein is thus necessary but not

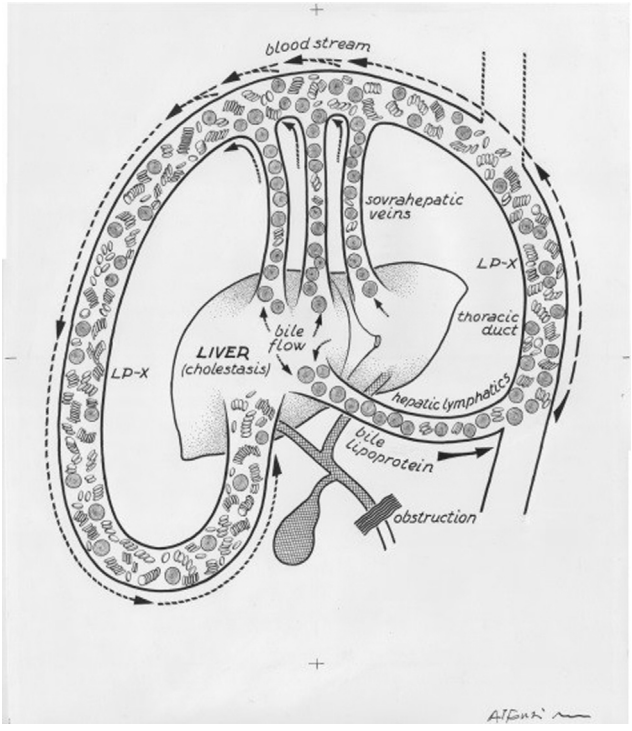

Figure 2 Lp-X derives from a "precursor" lipoprotein complex which is normally excreted by the liver into bile, but which refluxes under cholestatic conditions into the plasma where it associates with other plasma components to form Lp-X.

sufficient to obtain a “mature” Lp-X in plasma. The activity of the Mdr2 P-glycoprotein is essential for LpX appearance, since its suppression abolishes Lp-X formation [36]. However, the plasma concentration of Lp-X is also determined by the degree of the cholestasis, the residual liver function, and the LCAT deficiency.

In addition to Lp-X formation, a complex dyslipidemia characterized by reduced HDL and LCAT activity and higher LDL phospholipid and VLDL synthesis is reported in cholestatic patients [37]. In this clinical condition, bile acids activate FXRs that inhibit the APOA gene thus reducing the plasma Lp(a) concentration [7]. Lp-X formation seems to be independent from these abnormalities, but its presence in plasma has a role in the modifications of the other plasma lipoproteins.

During cholestasis, plasma phospholipid and cholesterol syntheses are increased, this latter due to an increase of hepatic HMG-CoA reductase activity. Lp-X is the main cause of the hypercholesterolemia in patients with cholestasis. Lp-X does not contain apoB, which is the most important ligand of the lipoproteins to the apo-B/LDL liver receptor. Due to the absence of apoB Lp-X is not internalized in the hepatocyte and thus it does not inhibit the activity of the HMG-CoA reductase, which is the rate limiting enzyme in the cellular cholesterol synthesis. The absence of inhibition of the HMG-CoA reductase may explain why cholesterol synthesis is increased during cholestasis in spite of the increased plasma concentrations of cholesterol [38,39]. Inhibition of the chylomicron remnant uptake by the liver could also contribute to the hypercholesterolemia in cholestatic patients [38].

Few data are available concerning Lp-X catabolism. A rapid, simultaneous decrease in Lp-X, an increase in esterified cholesterol and lysolecithin, and the appearance of HDL2 particles due to LCAT and phospholipase A activities occur in the plasma after biliary obstruction is surgically removed [40,41]. Lp-X is not removed by the apo-B/LDL receptor because apo-B is not present. Most of the Lp-X seems to be removed through the reticuloendothelial system while a smaller quantity may be removed by the hepatocytes through apoE binding. In an animal model with common biliary duct-caval vein anastomosis, large quantities of free cholesterol and phospholipids similar in ultrastructure to Lp-X accumulate in the sub-endothelial space of the kidney glomeruli thus indicating that the kidney is another important catabolic site for this particle [42].

Recent experimental data obtained in LCAT knock-out mouse (a condition similar to familial LCAT deficiency) demonstrated that the Lp-X present in these animals, which is similar to the cholestatic Lp-X, is nephrotoxic and thus causes kidney disease in this condition [43]. Glomerular damage was never demonstrated in humans with chronic cholestasis (e.g. primary biliary cholangitis).

Conclusion

Fifty years ago the description of Lp-X made it possible to understand the basis of the peculiar hypercholesterolemia of cholestasis and the following research activities resulted in a better understanding of the lipid metabolism in this condition. The Lp-X test may be useful to identify the presence of cholestasis in patients with liver abnormalities of uncertain origin. The findings outlined by Helferink et al., Bravo et al., and more recently Heimerl et al. [36,39,44] have confirmed the complexity of the mechanisms involved in Lp-X formation and the numerous metabolic perturbations produced during cholestasis.

Lp-X might be considered a defense mechanism against the toxic effect of free cholesterol and a primitive model of lipid transport in plasma (using albumin) before the appearance of specific apolipoproteins. The experimental and clinical data available show that Lp-X (rich in free cholesterol and phospholipids but without apoB) is not an atherogenic lipoprotein. Should it be the case, the hypercholesterolemia of cholestasis would be one condition of plasma cholesterol increase without associated vascular risk. In any case, the role of phospholipids as antiatherogenic molecules needs further elucidation and a better understanding of these mechanisms could provide new insights into atherosclerosis protection.

Among the several questions unanswered, one of the most relevant is an insufficient knowledge of the fine mechanisms of Lp-X formation and its role on lipid metabolism alterations during cholestasis. Now as we mark the 50th anniversary of its discovery it seems a good time to renew our interest on this topic.

Conflicts of interest

All authors declare no conflict of interest associated with this paper.

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