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Review article

Clinical Perspective Of Lipoprotein – X

Dr. Suchitra Kumari, Dr. Tarun Kumar Panda

Asst. Professor, Dept. Of Biochemistry, All India Institute Of Medical Sciences, Bhubaneswar-19, Odisha
Ophthalmic Surgeon, S.C.B. Medical College, Cuttack, Odisha

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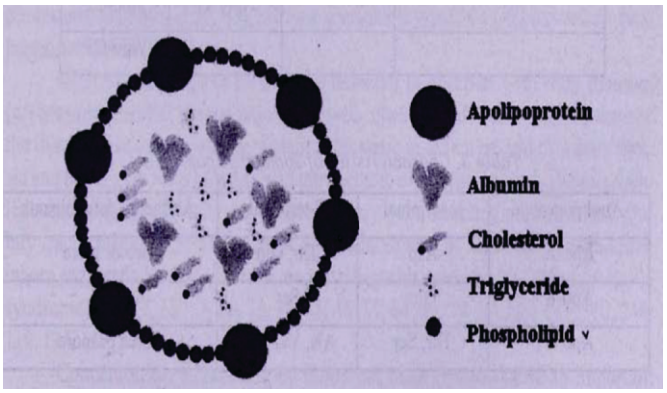
ABSTRACT

Lipoprotein – X(abnormal lipoprotein) is rich in phospholipids and unesterified cholesterol. The main protein component is albumin within the core and apolipoprotein C upon the surface. It is cleared by the reticuloendothelial system and the kidneys. Earlier studies reported presence of lipoprotein X (LP-X) in patients with cholestasis. Bile lipoprotein is a precursor of LP-X and in cholestasis this refluxes into the plasma pool , binds to albumin to form LP-X. Cholestasis of pregnancy and Primary biliary cirrhosis patients also reported high LP-X levels. LP-X may not be atherogenic and it may have antioxidant LDL activity. LP- X is found in LCAT deficiency which is characterised by low High Density Lipoprotein(HDL), anaemia , corneal opacity and chronic kidney diseases. The presence of serum LP-X can be associated with severe hyperlipidaemia , pseudohyponatremia and it also interfere with some serum LDLc assays and complexes with Alkaline phosphatase.

1. Introduction

In recent years abnormal lipoprotein ,termed as lipoprotein X (LP-X) has attracted considerable interest both because of its role in the study of the fundamentals of lipoprotein metabolism [1] and their significance in clinical diagnosis [2] .By ultra centrifugal floatation ,LP-X appears in the low density lipoprotein(LDL)fraction, however it differ strongly from normal low density lipoprotein (LDL) in its composition and properties. LP-X is a lamellar spherical particle with mean diameter 69 nm (range 40-100 nm) as revealed by electron microscope [3].It is rich in phospholipids (60-67%) i.e.Lysophosphatidylcholin (4.1%),Sphingomyelin(14.2%),Phosphatidylcholine(77.5%),Phosphatidylethanolamine(2.5%) and cholesterol(23-30%) but poor in cholesterol ester(0.5-2%) , triglycerides(2-3%) and protein(3-7%)[4,5].Bile acids often present in LP-X is lithocholic acid. The protein component of lipoprotein X is dominated by albumin located in the core and apolipoprotein C (I, II ,III) located on the surface of the particle [6,7]. Apolipoprotein C was discovered in 1964 by Gustafson and co workers[8]. Apolipoprotein C has domain containing amphipathic helix. Hydrophobic amino acids are located at one side of the helix and hydrophilic amino acids at the other side .The hydrophobic part of the helix is thought to interact with acyl chain of phospholipids whereas the hydrophilic part interacts with phospholipid hydrophilic group (figure-1).

Figure-1. Structure of Lipoprotein X



Hydroxyapatite chromatography exhibited that LP-X has a higher molecular weight compared to LDL [9] . Proton magnetic resonance studies showed motion of acyl chains and cholesterol rings restricted in LP-X compared to its normal counterpart(LDL) [10]. Table -1 and Table-2 shows the molecular composition of different lipoproteins. Using zonal ultracentrifugation , LP-X can be divided into three isoforms i.e. LP-X1 , LP-X2 and LP-X3 differing in density, phospholipid content and apolipoprotein composition [11] . Unlike low density lipoprotein , LP-X does not contain apolipoprotein B nor is it removed by LDL receptor but LP-X is cleared by the reticuloendothelial system and the kidneys.

* Corresponding Author : **DR SUCHITRA KUMARI , MBBS, MD**
Asst.professor, Department Of Biochemistry
All India Institute Of Medical Sciences (aiims)
Sijua, Dumduma
Bhubaneswar-751019, Khurda ,odisha,india
Tel: 9438884005(mob)
E Mail: Suchitrakumari76@gmail.com

Table-1.Molecular composition of Lipoproteins

Class	Protein (%)	Cholesterol (%)	Phospholipids (%)	Triacylglycerol (%)
HDL	33	30	29	8
LDL	25	50	21	4
LP-X	6	27	65	2
VLDL	10	22	18	50
CHYLOMICRON	<2	8	7	84

Table-2. Apolipoproteins in different Lipoproteins

VLDL	LDL	LP-X	HDL
Apo-B 100	Apo-B100		Apo-A1
Apo-C1		Apo -C1	Apo- A2
Apo-C2		Apo- C2	Apo-C1
Apo-C3		Apo- C3	Apo-C2
Apo-E			Apo-C3
Apo-D		Apo- E	
		Apo-A1	

LP-X was detected for the first time in the blood sample of the patients with liver disease with obstructive jaundice[12]. Subsequent studies revealed that LP-X is detected in 45% of cases of liver disease with cholestasis, hypercholesterolemia and hyperlipoproteinemia[13].The failure of LP-X to exert feedback inhibition on cholesterol synthesis may contribute to the mechanism of hypercholesterolemia in obstructive jaundice. The presence of serum lipoprotein X does not distinguish between intrahepatic and extrahepatic cholestasis, however the concentration of LP-X in in patients with extrahepatic cholestasis were significantly higher than in those with intrahepatic cholestasis [14]. Bile lipoprotein is a precursor of LP-X and in cholestasis this refluxes into the plasma pool and binds with albumin to form LP-X.Further investigation demonstrated presence of LP-X in the blood of patients with primary biliary cirrhosis , cholangitis , hepatic cirrhosis and cholestasis of pregnancy [5,15,16]. In graft versus host disease of the liver after allogenic bone marrow transplantation, plasma LP-X is associated with severe hypercholesterolemia and xanthelasma. LP-X was also detected in the blood of patients with acute viral (96% of patients with hepatitis A , 82% of hepatitis B) and toxic hepatitis. It was shown that in acute case of Viral hepatitis , LP-X is the most specific test in determining the presence of cholestasis [17].LP-X levels were detected higher in children with progressive familial intrahepatic cholestasis and in infants with persistant cholestatic jaundice caused by biliary atresia and biliary agenesis of extra and intrahepatic origin [18,19].Considering the plasma LP-X level as an important and informative marker of above mentioned liver and biliary diseases , its estimation has been widely used for clinical diagnosis of cholestasis and for monitoring the efficiency of relevant therapeutic measures [4,8, 19 20]. The study conducted by Stepien et al [21] confirms these earlier observations of raised serum LP-X in cholestasis but it is still debatable whether presence of LP-X in cholestasis increase cardiovascular risk. Perspective observation for a median of 7.4 years of 312 patients with primary biliary cirrhosis of various stages with highly increased cholesterol level , found no increased incidence of atherosclerotic death compared to age and sex matched controls [22].Based upon these results it was proposed that LP-X may be responsible for this phenomenon by preventing formation of oxidized LDL products and thus reducing LDL atherogenicity [23].In vitro study performed by Chang and Co workers[24] recently confirmed the above fact by revealing that after prolonged incubation with copper, LP-X containing LDL isolated from the blood of patients with primary biliary cirrhosis failed to increase the oxidation index or electrophoretic mobility noted in control LDL. These results suggest that LP-X reduces LDL atherogenicity by preventing LDL oxidation to protect endothelial cells integrity in hypercholesterolemia [24,25].They also suggested that altering LDL composition may be equally important as reducing LDL concentration in preventing or treating atherosclerosis.

Lecithin-cholesterol acyltransferase (LCAT, EC 2.3.1.43) is an enzyme which converts free cholesterol into cholesterol ester (a more hydrophobic form of cholesterol) which is sequestered into the core of a lipoprotein particle , making it a spherical structure. Familial LCAT deficiency is a monogenic autosomal recessive trait affecting cholesterol esterification , molecular basis being several allelic mutations of polymorphic gene on chromosome16 (16q 22.1) encoded LCAT [26,27,28]. This disease is characterized by diffuse corneal opacities ,target cell haemolytic anaemia (normocytic normochromic anaemia) , low concentration of high density lipoprotein(HDL) and renal dysfunction(proteinuria with renal failure) [29]. Familial LCAT deficiency is associated with low LDL and accumulation of LP-X in the plasma of patients [29,30,31]. The plasma concentration of LP-X in familial LCAT deficiency ranges from 43 mg/100 ml to 251mg/ 100 ml with a mean of 127 mg/ 100 ml. It is above the mean value of LP-X in patients with intrahepatic cholestasis (49 mg/ 100 ml) and below the mean level found in patients with extrahepatic cholestasis (341 mg / 100 ml) [32].The high level of LP-X cause glomerular capillary endothelial damage [33] and lead to progressive renal impairment followed by end stage renal failure [34].Lynn et al suggested that LP-X participates in the pathogenesis of glomerulosclerosis and subsequent renal failure in familial LCAT deficiency by stimulating monocyte infiltration via a mechanism involving the expression of MCP-1 (chemoattractant for monocytes) by mesangial cells [35], monocyte infiltration into the affected glomeruli being one of the key events in the pathogenesis of glomeruloscerosis in familial LCAT deficiency [36].Proteoglycans also plays an important role in regulating the uptake of LP-X into kidney mesangial cells and this mechanism is independant of the scavenger receptor [37].

Pseudohyponatremia has been reported in patients with severe hypercholesterolemia secondary to raised LP-X [38]. Siva kumar et al [39] described not only Pseudohyponatremia but also Pseudohypokalemia and Pseudohypochloridaemia in the presence of high concentration of LP-X. Assay bias has also been documented by various researchers for serum LDL cholesterol in the presence of LP-X. This should be considered while interpreting LDLc results in severely cholestatic serum samples [40,41]. Plasma concentration of LP-X was significantly correlated to the plasma activity of alkaline Phosphatase and serum bilirubin. Having strong aggregatory property ,LP-X can bind to alkaline phosphatase (ALP) producing a LPX -ALP complex. This complex is detected in hepatic malignancy induced cholestatic patients.

Starch gel electrophoresis of serum samples from patients with biliary obstruction revealed stationary band of ALP which was thought to be due to ALP binding to LP-X [42]. LP-X can bind and remove free cholesterol from the circulation due to its strong aggregating ability [43]. Agarose gel electrophoresis , ultracentrifugation , nuclear magnetic resonance spectroscopy and immunological techniques [44,45,46] are some of the assay techniques available to measure serum LP-X .Some assays utilize differential precipitation of apo B containing lipoproteins and unesterified cholesterol is measured.

To summarize, different studies revealed raised serum LP-X in cholestasis but it is still debatable whether presence of LP-X in cholestasis increase cardiovascular risk. Further presence of LP-X in cholestasis does not distinguish between intrahepatic and extrahepatic causes. LP-X may be responsible for preventing formation of oxidized LDL products and thus reducing LDL atherogenicity. Raised LP-X levels in LCAT deficiency and after intra venous infusion of intra lipid solution had also been reported. Pseudohyponatremia , Pseudohypokalemia as well asPseudohypochloridaemia were associated with severe hypercholesterolemia secondary to increased LP-X level. Assay bias for serum LDL cholesterol in the presence of LP-X , strong aggregating property of LP-X forming LPX- ALP complex are some of the important practical points to be consider while interpreting LDL cholesterol results in severely cholestatic serum sample.

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