

## Lipoprotein X in Cholestatic Disease: Case Report and Literature Review

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### Abstract

Cholestatic disease plays a major role among the secondary causes of hypercholesterolemia. In this condition high plasma cholesterol levels are generally related to the appearance of a peculiar particle rich in phospholipids and unesterified cholesterol, lipoprotein X, a non-atherogenic lipoprotein which was identified fifty years ago by Dietrich Seidel and Paul Alaupovic. Treatment of the condition relies on the correction of the underneath disease. On the other hand lipid lowering drugs, in particular HMG-CoA reductase inhibitors (statins), may prove ineffective or even toxic, given their catabolism largely by hepatic route. We hereby briefly outline the case of a young patient with extremely high plasma cholesterol levels related to liver disease.

**Keywords:** Hypercholesterolemia; Non-Atherogenic Lipoprotein; Lipoprotein X; Cholestatic Diseases; Liver Disease

### Abbreviations

Lp-X: Lipoprotein X; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; EBV: Epstein Barr Virus; CMV: Cytomegalovirus

### Introduction

Hypercholesterolemia has been widely recognized as a major cardiovascular risk factor and its evaluation is part of a comprehensive clinical assessment [1]. It may be a primary metabolic abnormality or a secondary condition, related to several disorders. In hepatic cholestasis it represents a common marker of this disease if moderately-high lipid values are considered, and it often associates with mild to severe hypertriglyceridemia. It has not been stated a definite relationship with accelerated atherosclerosis, given its transitory course or an unfavorable prognosis related to the causative disease. A prominent increase in plasma cholesterol may sometimes be apparent, and this condition is dependent on a peculiar and abnormal lipoprotein particle, which has been defined lipoprotein X (Lp-X). It was identified half a century ago by two eminent lipidologists, Dietrich Seidel and Paul Alaupovic, at the Oklahoma Medical Research Foundation [2] while its composition and production was definitely assessed by Renato Fellin and Enzo Manzato a decade later [3,4].

### Case Report

A 34 year-old black man addressed the Emergency Department of Ferrara Hospital for a recent history of increased abdominal girth, abdominal colic pain, diarrhea, dark urine, jaundice and itching. He came from Ghana, had been living in Italy for 7 years and denied travelling abroad in the last twelve months. His past medical history was unremarkable; he reported occasional unprotected sex and intake of only small alcohol amounts. His vital signs were normal with the exception of slight fever; he presented scleral icterus and distended abdomen painful at palpation while lower liver edge extended 3 - 4 centimeters below the costal margin; no flapping tremor or other signs of hepatic failure were present. Hematochemical parameters showed anemia (Hb 9.5 g/dl) and thrombocytopenia (126.000/ $\mu$ l),

increase in total bilirubin (20 mg/dl, conjugated bil. 9 mg/dl), alanine and aspartic aminotransferases (ALT, 98 IU/l and AST, 226 IU/l, respectively), gamma-glutamyl transferase (GGT, 4795 IU/L,) and alkaline phosphatase (ALP, 1087 IU/L), ammonium (123 mmol/l); the lipid profile disclosed a prominent increase in total cholesterol (1.129 mg/dl) and only slightly hypertriglyceridemia (208 mg/dl) while HDL cholesterol (45 mg/dl) and apolipoprotein B (103 mg/dl) were within normal limits and apolipoprotein A-I was decreased (< 40 mg/dl). Antinuclear antibody screening was normal and serologic testing for the major hepatotropic viruses were indicative of past-infection (Hepatitis A virus, HAV, Hepatitis B virus, HBV, Hepatitis C virus, HCV, Epstein Barr virus, EBV, Cytomegalovirus, CMV); Wilson disease and hemochromatosis were similarly excluded. Abdominal Ultrasound findings disclosed ascites, hepatomegaly with diffusely increased echogenicity and enlarged lymph nodes at the hepatic hilum; endoscopy showed mild congestive gastropathy. The Serum-Ascites Albumin Gradient (SAAG) was 2.8, suggestive of portal hypertension, while cultural and cytologic evaluation of peritoneal fluid proved negative. During hospitalization, furosemide, canrenone, lactitol and branched-chain amino acids were administered. At the time of discharge, after 12 days from hospital admission, the clinical conditions were satisfactory and no abdominal effusion was still apparent; serum bilirubin decreased (7.7 mg/dl, conjugated bilirubin 3.7 mg/dl) and the lipid profile improved (total cholesterol 798 mg/dl, triglycerides 206 mg/dl, HDL cholesterol 70 mg/dl). Outpatient re-evaluation one month later, showed further reduction of total bilirubin concentration (2.67 mg/dl), GGT (339 U/L), total cholesterol (436 mg/dl) and HDL cholesterol (56 mg/dl) with stable serum triglyceride (146 mg/dl) (Table 1). Lipoprotein profiling was performed by non-denaturing polyacrylamide gel-tube electrophoresis (Lipoprint; Quantimetrix Corporation, CA, US) [5] and it disclosed a band above LDLs compatible with Lp-X. Unfortunately, the patient did not presented to a successive visit and he was missed at follow-up.

Blood testing	During hospitalization			One month later
Serum sodium (136 - 145 mmol/l)	132	132		134
Total bilirubin (< 1.2 mg/dl)	20.27	19.16	12.86	2.67
Conjugated bilirubin (< 0.3 mg/dl)	9.58	9.85	6.52	1.3
AST (< 50 UI/l)	226	169		50
ALT (< 50 UI/l)	84	69		38
GGT (< 55 UI/l)	4795	4688	2497	339
Total cholesterol (100 - 200 mg/dl)	1129	969	797	436
HDL cholesterol (35 - 70 mg/dl)	45	43		
Triglyceride's (50 - 150 mg/dl)	208	186		
Apolipoprotein A-I (105 - 175 mg/dl)	< 40			
Apolipoprotein B (60 - 110 mg/dl)	103			
Ammonium (< 53 mcmol/L)	92		32	

**Table 1:** Liver function and lipid parameters.

Given the above results, we are quite confident in excluding the main liver-affecting infectious, autoimmune, congenital and neoplastic disease, even in the absence of a histologic examination. A self-reporting but ill-defined alcohol assumption in spite of a negative history of drug or other toxic substance abuse, and a slow but progressive clinical and biochemical improvement after ethanol withdrawal, suggests a diagnosis of alcohol-related intrahepatic cholestasis.

## Discussion

This case of severe hypercholesterolemia, even higher than homozygous genetic forms, may be classified as a secondary dyslipidemia seemingly related to alcohol abuse and characterized by the appearance of Lp-X in plasma. In 1862 Flint described the association between hypercholesterolemia and obstructive jaundice, but it was only in 1969 that Seidel, *et al.* isolated for the first time the causative lipoprotein, which they named Lp-X. Lp-X is a lamellar spherical particle (about 50 nm diameter), rapidly catabolized by the liver and composed primarily of lipids (phospholipids, 65%, and free cholesterol), albumin and small amounts of apolipoprotein A-1, C, and E, but not containing apolipoprotein B [6]. Lipoprotein lipase, part of the lipoprotein degradation system, is inhibited by bile acids, so in cholestatic liver diseases the reflux of bile in plasma favors the formation and inhibits the catabolism of Lp-X; besides a reduction in cholesterol acyltransferase (LCAT) activity, common in patients with a hepatocellular disease, promotes the accumulation of phospholipid and free cholesterol in this particle [7]. Since lacking apolipoprotein B, Lp-X is resistant to hepatic LDL-receptor clearance, and its cholesterol doesn't exert negative feedback on intracellular sterol biosynthesis [8]. Lp-X may be found in pregnancy, a para-physiological condition, but it is more properly a clue of some more severe pathologic conditions: graft-versus-host disease (GVHD), lecithin cholesterol acyltransferase (LCAT) deficiency and cholestasis disease, (in particular in the context of primary biliary cholangitis, PBC [9]). Intrahepatic cholestasis is not an uncommon condition during pregnancy. It is characterized by an increase in plasma concentration of bile salts and induces disturbing itching. It was already 40 years ago that Johnson, *et al.* studied 39 pregnant women with compatible symptoms [10] finding Lp-X as a plasma marker and highlighting the role of abnormal liver response to estrogens as the causative agent. GVHD of the liver, a complication of allogeneic hematopoietic cell transplant, presents with abnormal liver tests, including conjugated bilirubin and alkaline phosphatase, but also serum cholesterol increase; although moderately-high blood cholesterol may be a secondary effect of immunosuppressive therapies (e.g. ciclosporin, tacrolimus, etc.), some clinical cases with GVHD and extreme hypercholesterolemia due to Lp-X have been reported. Turchin, *et al.* described 3 such cases in patients with chronic GVHD of the liver (confirmed by biopsy) after an allogeneic bone marrow transplantation [11]: in one of these subjects, the lipid profile was characterized by particularly high total cholesterol (1836 mg/dl), with normal HDL-cholesterol (51 mg/dl) and triglycerides (136 mg/dl) while agarose gel electrophoresis of ultracentrifugated serum fractions showed the presence of Lp-X. No concomitant atherosclerotic manifestation of the lipid disorder was reported, and plasma levels decrease while actively treating GVHD or, after plasmapheresis; however, one of these cases disclosed retinal cholesterol thromboembolism, xanthoma and a cholesteroloma of the lung, in complete remission after therapy. Low plasma levels of LCAT, an enzyme responsible for esterification of free lipoprotein cholesterol, is associated with two peculiar conditions: LCAT deficiency and fish eye disease. The first one is characterized by anemia, corneal opacities and proteinuria or nephropathy; in this context Lp-X like proteins cross the glomerular endothelial barrier, accumulate in the mesangium with subsequent disruption of the glomerular basement membrane, causing renal failure [12]. Primary biliary cholangitis (PBC) is an autoimmune disease in which T-lymphocytes mediate small intralobular bile duct damage, cholestasis with lately appearance of cirrhosis and liver failure. Even in presence of a reduction in synthesis of bile acids (and therefore a diminished intestinal cholesterol absorption) and lipoproteins, markedly high cholesterol levels may be found [13]. The reason seems the same: a falling hepatic clearance of Lp-X responsible for its increasing plasma levels. In this setting several clinical studies disclose serum total cholesterol levels between 112 and 1779 mg/dl [6]; Wong, *et al.* reported the case of a young woman with a serum total cholesterol of 3204 mg/dl at the onset of this disease; she was treated during the following 40 months with regular plasmapheresis for a lipoprotein-related hyperviscosity syndrome [14]. Most studies on the apparent "paradox" of Lp-X related high plasma cholesterol and a not-increased incidence of cardiovascular disease have been performed in PBC. The reason is still uncertain but probably dependent on some anti-atherogenic properties of Lp-X [15]. Chang, *et al.* presented evidence that Lp-X is resistant to oxidation and may also exert antioxidant properties because it should prevent LDL modification and damaging vascular endothelial cells [16]; in addition other anti-atherogenic characteristics may be represented by low apo-B concentration and absence of LDL receptor interactions. With a few exceptions Lp-X increase is generally asymptomatic (within the sphere of the underneath disease) or it may cause hyperviscosity syndrome (as previously described) or pseudo-hyponatremia; Hussain, *et al.* reported a case of a woman affected by PBC with elevated cholesterol (2415 mg/dl) and apparent severe hyponatremia, but normal serum osmolality (sodium 121 mmol/l, 296 mOsm) since the effective distribution volume of water-soluble chemicals was reduced by the insoluble lipids [17]. Since LDL and Lp-X share a similar density, they result almost indistinguishable after standard ultracentrifugation, causing errors of interpretations in com-

mon clinical practice. Various techniques could be used to measure Lp-X: agarose gel electrophoresis, ultracentrifugation, polyacrylamide gradient-gel electrophoresis, nuclear magnetic resonance spectroscopy and immunological techniques [4,18,19]; after ultracentrifugation and electrophoretic analysis of serum it is possible to detect some discrete subpopulations. Also plasma apolipoprotein B measurement is helpful in diagnosis, since it doesn't increase when high cholesterol values are related to high Lp-X plasma levels. Hypercholesterolemia improves with cholestasis treatment and lipid-lowering drugs are unnecessary because both ineffective and possibly toxic (most of them are normally secreted into bile).

### Conclusion

In conclusion severe hypercholesterolemia in a person with previous normal value should always alert that a secondary condition be present; we maintain that alcohol abuse should be included among the disorders causing abnormal Lp-X increase, at least when cholestatic hepatitis was a complication.

### Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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