

Lipoprotein X: artifactual lipid derangement in type 3c diabetes with obstructive liver disease

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Abstract

Lipoprotein X is an abnormal lipoprotein formed in cholestatic liver disease that causes artifactual elevation of calculated and measured direct low-density lipoprotein cholesterol (LDL-C). A 40-year-old man with chronic pancreatitis presented with hyperglycemic hyperosmolar state secondary to type 3c diabetes. He was jaundiced, with total bilirubin of 9.4 mg/dL (SI: 161 μ mol/L) (reference range, 0.3–1.4 mg/dL [SI: 5–24 μ mol/L]). Abdominal computed tomography showed severe common bile duct stricturing causing obstructive cholestasis. Laboratory results revealed a physiologically implausible lipid profile: total cholesterol (TC) of 1531 mg/dL (SI: 39.6 mmol/L) (desirable concentration, <200 mg/dL [SI: <5.2 mmol/L]) and direct LDL-C of 1636 mg/dL (SI: 42.3 mmol/L) (desirable concentration, <100 mg/dL [SI: <2.6 mmol/L]). Low-density lipoprotein cholesterol exceeding TC indicated analytical interference. Apolipoprotein B (ApoB) was elevated: 278 mg/dL (SI: 2.78 g/L) (reference range, 66–144 mg/dL [SI: 0.66–1.44 g/L]). The TC:ApoB ratio was 6.9 mmol/g (reference range, 3.8–6.3 mmol/g), supporting coexistent ApoB-negative lipoprotein. Liver and lipid parameters improved post-biliary stenting. ApoB normalized at 6 weeks, supporting a transient, insulin-deficiency-related ApoB-containing lipoprotein excess. Clinicians should suspect lipoprotein X when LDL-C exceeds TC in the setting of cholestasis; if ApoB is also elevated, transient ApoB-mediated dyslipidemia may coexist. Management centers on correcting underlying biliary and metabolic pathology.

Key Words lipidology, lipoprotein, cholestasis

Introduction

In clinical endocrinology, extreme hypercholesterolemia is often attributed to familial hypercholesterolemia (FH) or to severe metabolic derangement. In acute insulin-deficient hyperglycemic decompensation such as diabetic ketoacidosis or hyperosmolar hyperglycemic state, adipose lipolysis, increased hepatic free fatty acid flux, very low-density lipoprotein (VLDL) overproduction, and impaired lipoprotein clearance can produce a transient dyslipidemia [1]. However, obstructive jaundice can lead to the formation of lipoprotein X (LpX), an abnormal lamellar lipoprotein rich in free cholesterol and phospholipids. Lipoprotein X lacks apolipoprotein B (ApoB), so it is distinct from low-density lipoprotein (LDL). However, cholesterol within LpX can interfere significantly with both calculated and direct LDL cholesterol (LDL-C) assays, leading to spuriously elevated results [2]. Lipoprotein X

is most commonly associated with cholestatic liver disease, including benign or malignant biliary obstruction, but has also been described in lecithin-cholesterol acyltransferase deficiency and, less commonly, in patients receiving total parenteral nutrition. Although LpX has not been linked to increased risk for cardiovascular disease, its accumulation may have important clinical consequences, including cutaneous xanthomas and, in severe cases, hyperviscosity syndrome [3]. This case highlights the diagnostic challenge of identifying LpX in the context of concurrent cholestasis and acute hyperglycemic decompensation.

Case presentation

A 40-year-old man with a history of alcohol-induced chronic pancreatitis and pancreatic pseudocysts presented to the

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emergency department with a 2-month history of pale stools, dark urine, and 30 kg unintentional weight loss over the preceding 5 weeks. Additionally, he reported new osmotic symptoms of polyuria, polydipsia, and blurred vision over the preceding 2 weeks. He had a history of significant alcohol use but had been abstinent for the past 2 years. His medical history also included type 2 diabetes diagnosed 1 year prior, hypertension, and epilepsy. He had established exocrine pancreatic failure, on pancreatin replacement, and had commenced metformin 1 g twice daily for 6 months prior to presentation. He was hemodynamically stable and afebrile, with a heart rate of 82 beats per minute, blood pressure of 147/92 mmHg, respiratory rate of 17 breaths per minute, and oxygen saturation of 99% on room air. He was noted to be jaundiced and had mild epigastric tenderness, but physical examination was otherwise unremarkable.

Diagnostic assessment

Venous blood gas at presentation revealed significant hyperglycemia: blood glucose of 522 mg/dL (SI: 29 mmol/L) (nondiabetic range, <200 mg/dL [SI: <11.1 mmol/L]). He had mild ketosis (25 mg/dL [SI: 2.4 mmol/L]) (reference range, <6 mg/dL [SI: <0.6 mmol/L]) but was not acidotic: pH of 7.46 (reference range, 7.35-7.45) and venous bicarbonate of 27.9 mEq/L (SI: 27.9 mmol/L) (reference range, 22-29 mEq/L [SI: 22-29 mmol/L]). Serum osmolality was elevated at 304 mOsm/kg (reference range, 285-295 mOsm/kg). Glycated hemoglobin (HbA1c) was 15.9% (SI: 150 mmol/mol) (diagnostic threshold for diabetes, $\geq 6.5\%$ [SI: ≥ 48 mmol/mol]), consistent with severe hyperglycemia. Given his history of alcohol-related chronic pancreatitis with exocrine pancreatic failure and clinical symptoms of progressive endocrine pancreatic failure, his diabetes was reclassified as type 3c (pancreatogenic) diabetes.

Liver biochemistries showed a cholestatic pattern (Table 1), with total bilirubin of 9.4 mg/dL (SI: 161 μ mol/L) (reference range, 0.3-1.4 mg/dL [SI: 5-24 μ mol/L]), alanine aminotransferase of 82 IU/L (reference range, 0-55 IU/L), alkaline phosphatase of 941 IU/L (reference range, 30-130 IU/L), and gamma-glutamyl transferase of 3657 IU/L (reference range, 11-67 IU/L). This represented a significant elevation in liver biochemistries from 7 months prior to admission: total bilirubin of 1.3 mg/dL (SI: 22 μ mol/L), alanine aminotransferase of 31 IU/L, alkaline phosphatase of 112 IU/L, and gamma-glutamyl transferase of 348 IU/L. Abdominal computed tomography demonstrated stricture of the common bile duct with intra- and extrahepatic biliary dilatation, consistent with obstructive cholestasis. There was a slight reduction in the size of the longstanding multifocal pseudocysts in the head of the pancreas, and no new lesion was visualized at the pancreatic head.

During admission, a lipid profile was obtained as part of evaluation for chronic pancreatitis. This showed extreme hypercholesterolemia with discordant results, including LDL-C exceeding total cholesterol (TC): TC of 1531 mg/dL (SI: 39.6 mmol/L) (desirable concentration, <200 mg/dL [SI: <5.2 mmol/L]) and direct LDL-C of 1636 mg/dL (SI: 42.3 mmol/L) (desirable concentration, <100 mg/dL [SI: <2.6 mmol/L]) [4], a physiologically implausible pattern strongly suggestive of analytical interference (Table 1). The Dutch Lipid Clinic Network score was 8 (probable FH) [5]

due to elevated LDL-C; however, there was no supportive family history of premature cardiovascular disease or clinical stigmata such as tendon xanthomas, xanthelasma, or corneal arcus. Furthermore, a lipid profile 7 months before admission had shown only modest dyslipidemia (TC of 209 mg/dL [SI: 5.41 mmol/L] and LDL-C of 146 mg/dL [SI: 3.78 mmol/L]).

Additional testing was requested to clarify whether the markedly elevated LDL-C reflected cholesterol present within true ApoB-containing LDL-C or ApoB-negative LpX. Apolipoprotein B was elevated at 278 mg/dL (SI: 2.78 g/L) (reference range, 66-144 mg/dL [SI: 0.66-1.44 g/L]), confirming coexisting excess ApoB-containing lipoproteins. However, the TC:ApoB ratio was also elevated at 6.9 mmol/g (male reference range, 3.8-6.3 mmol/g), suggesting that a proportion of cholesterol was carried in ApoB-negative particles consistent with LpX [2, 6]. Lipoprotein fractionation further supported this, as VLDL cholesterol (VLDL-C) was 298 mg/dL (SI: 7.7 mmol/L) (desirable concentration, <39 mg/dL [SI: <1.0 mmol/L]) despite an acceptable nonfasting triglyceride concentration of 160 mg/dL (SI: 1.81 mmol/L) (desirable concentration, <175 mg/dL [SI: <2.0 mmol/L]) [7], a discordance suggestive of interference from the presence of LpX, rather than true triglyceride-rich VLDL-C [2, 3, 6].

Treatment

The patient was treated for hyperosmolar hyperglycemic state with intravenous fluids, potassium replacement, and a variable rate intravenous insulin infusion, as per local treatment protocols. Once ketonemia had resolved, he was transitioned to a multiple daily injection regimen of subcutaneous insulin and educated on self-administration. He underwent urgent endoscopic retrograde cholangiopancreatography and biliary stenting.

Outcome and follow-up

Following biliary stenting, as the biliary obstruction resolved, both bilirubin and cholesterol levels declined in tandem (Fig. 1). Interval monitoring 6 weeks post-stenting demonstrated near-normalization of liver biochemistries and normalization of the lipid profile and ApoB: 85 mg/dL (SI: 0.85 g/L) (Table 1). HbA1c improved significantly to 8.1% (SI: 65 mmol/mol).

Discussion

Markedly elevated LDL-C usually raises concern for FH. In cholestasis, however, LpX may accumulate, resulting in elevated cholesterol, which may be measured as LDL-C by routine methods. Lipoprotein X is a 30 to 70 nm lamellar particle rich in phospholipids and free cholesterol, containing albumin but lacking ApoB. It has density similar to LDL, and size similar to VLDL, but is cleared mainly by the reticuloendothelial system and kidneys rather than via the LDL receptor [2, 3].

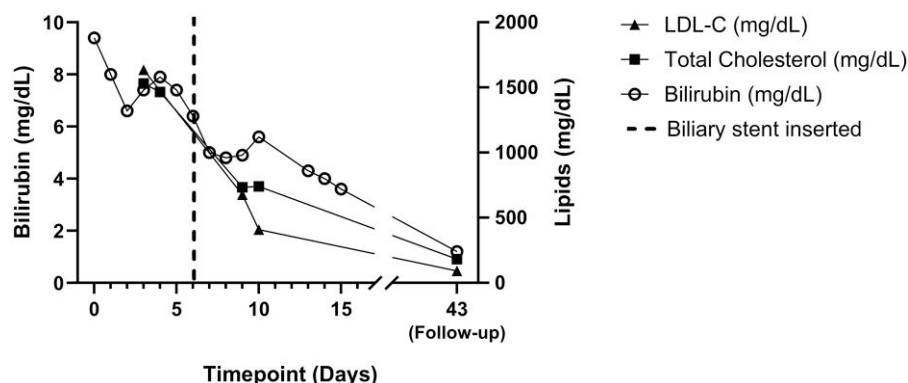
Lipoprotein X formation in cholestasis is thought to reflect reflux of biliary lipid fractions into plasma, where they associate with phospholipids, albumin, triglycerides, free cholesterol, ApoC, and ApoE [2, 3, 6]. It is reported in primary sclerosing cholangitis, primary biliary

Table 1 Liver biochemistry and lipid parameters during hospital admission and outpatient follow-up

Analyte	Reference interval and ^a desirable concentrations	Day 3	Day 9 (day 3 post-ERCP)	Day 10 (day 4 post-ERCP)	6-week follow-up (post-ERCP)
Liver biochemistries					
Total bilirubin	0.3-1.4 mg/dL (5-24 µmol/L)	7.4 mg/dL (126 µmol/L)	4.9 mg/dL (84 µmol/L)	5.6 mg/dL (95 µmol/L)	1.2 mg/dL (20 µmol/L)
AST	19-42 IU/L	78 IU/L	ND	ND	37 IU/L
ALT	<55 IU/L	88 IU/L	108 IU/L	107 IU/L	27 IU/L
ALP	30-130 IU/L	846 IU/L	634 IU/L	532 IU/L	134 IU/L
GGT	11-67 IU/L	4076 IU/L	2915 IU/L	2646 IU/L	149 IU/L
Albumin	3.5-5.0 g/dL (35-50 g/L)	3.7 g/dL (37 g/L)	3.0 g/dL (30 g/L)	3.1 g/dL (31 g/L)	4.7 g/dL (47 g/L)
Lipid profile					
TC ^a	<200 mg/dL (<5.2 mmol/L)	1531 mg/dL (39.6 mmol/L)	735 mg/dL (19.0 mmol/L)	741 mg/dL (19.16 mmol/L)	182 mg/dL (4.7 mmol/L)
TG ^a	<175 mg/dL (<2.0 mmol/L)	225 mg/dL (2.54 mmol/L)	67 mg/dL (0.76 mmol/L)	160 mg/dL (1.81 mmol/L)	47 mg/dL (0.53 mmol/L)
HDL-C ^a	>40 mg/dL (>1.0 mmol/L)	80 mg/dL (2.06 mmol/L)	43 mg/dL (1.12 mmol/L)	35 mg/dL (0.90 mmol/L)	80 mg/dL (2.06 mmol/L)
LDL-C ^a	<100 mg/dL (<2.6 mmol/L)	1636 mg/dL (42.3 mmol/L)	677 mg/dL (17.5 mmol/L)	410 mg/dL (10.6 mmol/L)	93 mg/dL (2.4 mmol/L)
VLDL-C ^a	<39 mg/dL (<1.0 mmol/L)	ND	ND	298 mg/dL (7.7 mmol/L)	ND
ApoB	66-144 mg/dL (0.66-1.44 g/L)	ND	ND	278 mg/dL (2.78 g/L)	85 mg/dL (0.85 g/L)

Results were obtained from nonfasting samples. Abnormal values are shown in bold font. Values in parentheses are International System of Units (SI). Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ApoB, apolipoprotein B; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ND, no data; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

^aFor lipid analytes, desirable concentrations are shown rather than conventional laboratory reference intervals.

**Figure 1** Trend in bilirubin, total cholesterol, and LDL-C prior to and following biliary stenting.

cholangitis, cholestasis of pregnancy, and hepatic graft-vs-host disease, and concentrations decline after relief of biliary obstruction [2]. Additionally, in lecithin-cholesterol acyltransferase deficiency, LpX can form because impaired cholesterol esterification disrupts free-cholesterol transport and high-density lipoprotein cholesterol formation [6, 8]. Rarely, LpX has been reported to occur in patients treated with lipid emulsion parenteral nutrition [3].

Distinguishing cholesterol within LpX from LDL-C is important because cardiovascular risk and treatment differ. Low-density lipoprotein cholesterol calculated by the Friedewald equation is invalid when LpX is present, as LpX cholesterol is misclassified

as LDL-C [2]. Apolipoprotein B can help because LpX lacks ApoB; therefore, high LDL-C with normal or disproportionately low ApoB supports LpX rather than true LDL excess [3, 6]. In this case, ApoB was elevated at 278 mg/dL (SI: 2.78 g/L), consistent with concurrent ApoB-containing lipoproteins, but remained disproportionate to the extremely elevated TC. The elevated TC: ApoB ratio supported the presence of cholesterol carried in ApoB-negative particles, consistent with LpX [2, 6]. The apparently cholesterol-rich, triglyceride-poor pattern seen on lipoprotein fractionation was compatible with the known composition of LpX, further supporting the presence of LpX [2, 3, 6]. Agarose

gel electrophoresis can be used to identify a characteristic LpX band, although this is not always present, and direct LpX measurement is not widely available [2].

In this case, elevated ApoB at presentation indicated that the lipid abnormality was not due to isolated LpX. Progressive endocrine pancreatic failure with extreme hyperglycemia likely caused acute-on-chronic insulin deficiency, increasing adipose lipolysis, hepatic free fatty acid flux, and VLDL-C production while impairing lipoprotein clearance. Coexisting cholestasis-related LpX and metabolic dysregulation therefore produced both analytical interference and a transient ApoB-mediated component. Normalization of ApoB and LDL-C 6 weeks after endoscopic retrograde cholangiopancreatography supports this interpretation and argues against persistent dyslipidemia.

Despite often extreme total cholesterol elevations, current clinical evidence does not support increased cardiovascular risk attributable to LpX itself. However, LpX is not biologically inert: it may cause xanthomas and, rarely, hyperviscosity syndrome. Suzuki et al showed that LpX isolated from cholestatic patients can induce foam-cell formation in human macrophages, possibly through ApoB-independent scavenger receptor pathways [9, 10]. Nevertheless, these mechanistic findings have not been matched by convincing clinical evidence of increased cardiovascular events, and the recognized complications of marked LpX excess remain xanthomatosis and hyperviscosity rather than accelerated atherosclerotic disease [10, 11].

Recognition of LpX is important to avoid erroneous FH diagnosis and inappropriate long-term lipid-lowering therapy. Standard lipid-lowering drugs are generally ineffective; management should focus on correcting cholestasis. Statins should be used cautiously in active cholestasis as impaired biliary excretion may increase exposure and risk of hepatotoxicity. Ezetimibe is generally ineffective because micellar cholesterol absorption is impaired [6], and fibrates are not considered first-line. In rare severe hyperviscosity, plasmapheresis may be used temporarily while definitive treatment is arranged [3, 6].

This case is noteworthy because LpX did not present as isolated ApoB-discordant hypercholesterolemia. Instead, cholestasis-related LpX coexisted with transient ApoB-containing lipoprotein excess during acute hyperglycemic metabolic decompensation, producing both implausible LDL-C results and a misleadingly elevated ApoB. Recognition of this composite pattern, and its resolution after biliary drainage and metabolic stabilization, prevented misclassification as FH and unnecessary long-term lipid-lowering therapy.

Learning points

- Direct LDL-C values exceeding total cholesterol should prompt consideration of LpX interference in the setting of cholestatic liver disease.
- In patients with acute insulin-deficient hyperglycemic decompensation such as diabetic ketoacidosis and hyperosmolar hyperglycemic state, ApoB may be transiently elevated. Where elevated ApoB and LpX are suspected to coexist, the TC:ApoB ratio can help distinguish ApoB-containing lipoprotein excess from LpX-related artifact.
- Recognition of LpX is essential to avoid unnecessary long-term lipid-lowering therapy, as LpX has not been shown to

increase cardiovascular risk. Management should focus on resolution of the underlying biliary obstruction, following which lipid parameters typically normalize rapidly.

Contributors

All authors made individual contributions to authorship. D.G. and A.P.K. were involved in diagnosis and management of the patient. P.M.O., B.B., G.R.L., and E.B. were involved in biochemical analysis. All authors reviewed and approved the final draft.

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Disclosures

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Informed patient consent for publication

Signed informed consent obtained directly from the patient.

Data availability

Original data generated and analyzed during this study are included in this published article.

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