

CASE REPORT

ADVANCED

CLINICAL CASE

Lipoprotein-X and Lipoprotein-Z Induced Hyperviscosity Syndrome in the Setting of Cholestatic Liver Failure



Ori Waksman, MD,^a Daniel J. Cho, BA,^b HyoungSup Kim, PhD,^b James D. Otvos, PhD,^c Robert S. Rosenson, MD^a

ABSTRACT

We describe a case referred for worsening hypercholesterolemia in the setting of atorvastatin and fenofibrate-induced liver injury. The patient reported neurological complaints attributed to hyperviscosity syndrome (induced by lipoprotein-X and lipoprotein-Z). Hepatic recovery was associated with reduction of whole blood viscosity and amelioration of neurological symptoms. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:1348-1352)

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HISTORY OF PRESENTATION

A 43-year-old female was referred for proprotein convertase subtilisin/kexin type 9 inhibitor therapy for worsening hypercholesterolemia in the setting of atorvastatin and fenofibrate-induced liver injury. A Model for End-stage Liver Disease score was 23. The patient reported debilitating neurological symptoms

including fatigue, blurred vision, paresthesia, and gait ataxia. Physical examination revealed jaundice, scleral icterus, and right upper quadrant abdominal tenderness.

PAST MEDICAL HISTORY

The patient's past medical history was notable for obesity as evidenced by a body mass index of 31 kg/m². She was hospitalized for recurrent episodes of acute pancreatitis on 3 occasions in the preceding 6 months. At the time of the first hospitalization, the triglyceride (TG) level was 3,140 mg/dL and non-high-density lipoprotein-cholesterol (HDL-C) 485 mg/dL. At this time, she was diagnosed with new-onset diabetes mellitus as evidenced by multiple fasting blood glucose measurements exceeding 126 mg/dL. The patient was fasted, and was administered intravenous fluids and insulin for 24 hours. Atorvastatin 20 mg and fenofibrate 140 mg were initiated upon hospital discharge. A lipid panel from 1 year prior

LEARNING OBJECTIVES

- To recognize the associations between severe liver injury and the presence of abnormal lipoproteins LP-X and LP-Z.
- To understand that LP-Z and LP-X elevations reflect erroneously elevated cholesterol measurements, which may not warrant lipid lowering pharmacotherapy.
- To recognize the association of LP-X and LP-Z with hyperviscosity syndrome, and the management of the condition.

From the ^aMetabolism and Lipids Unit, Cardiovascular Institute, Marie-Josée and Henry R Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, USA; ^bRheovector LLC, King of Prussia, PA, USA; and the ^cLaboratory Corporation of America (Labcorp) Holdings, Morrisville, North Carolina, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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revealed total cholesterol of 181 mg/dL, low-density lipoprotein-cholesterol (LDL-C) of 84 mg/dL, HDL-C of 58 mg/dL, non-HDL-C of 123 mg/dL and TG of 224 mg/dL. She otherwise had no other active medical conditions and was not prescribed or taking any medications.

After 2 months of atorvastatin and fenofibrate therapy, the patient developed malaise, nausea, and jaundice prompting a return hospital visit where she was found to have severe cholestatic liver injury and rising cholesterol levels including: total cholesterol of 565 mg/dL, LDL-C of 662 mg/dL, and TG of 416 mg/dL. Liver biopsy confirmed drug-induced liver failure. Subsequent imaging of the liver was notable for nonobstructive cholelithiasis along with biliary stricture and hematoma which were secondary complications of the biopsy. Other medical history was noncontributory.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included familial hypercholesterolemia vs mixed hyperlipidemia vs secondary hypercholesterolemia from cholestatic liver disease.

INVESTIGATION

Given the severe elevation of cholesterol in the setting of cholestatic liver injury, the presence of lipoprotein X (LP-X) and LP-Z was suspected.¹ As most commercial laboratory tests do not detect LP-X and LP-Z, a nuclear magnetic resonance (NMR) lipoprotein analysis was performed (Labcorp Holdings). The neurologic complaints of blurred vision, paresthesia, and gait ataxia were concerning for hyperviscosity syndrome. Whole blood viscosity (WBV) was measured with a Rheovector scanning capillary viscometer and serum viscosity was measured by a capillary viscometer.

Hepatic panel, WBV, serum viscosity, and NMR analyses were obtained on 2 separate visits. The NMR spectral deconvolution at the initial visit revealed discordance between measured and calculated serum lipid methyl signals (Figure 1A) that resolved when LP-X and LP-Z were included in the model (Figure 1B), indicating the presence of these abnormal lipoproteins. The presence of LP-X and LP-Z were associated with increases of WBV and serum viscosity, NMR analysis of the serum specimen obtained at the subsequent visit revealed large reductions in LP-X and LP-Z concentrations. WBV and serum viscosity decreased to reference range with resolution of neurological complaints.

MANAGEMENT

Following NMR analysis confirming presence of LP-X and LP-Z, lipid-lowering pharmacotherapies were not initiated due to historical lipid values that were inconsistent with familial hypercholesterolemia.²

Based on improving hepatic markers, conservative measures aimed at TG reduction to reduce risk of further pancreatitis were implemented including strict low-fat and carbohydrate-restricted diet and avoidance of hepatotoxic medications and alcohol. Vitamin D supplementation with ergocalciferol 50,000 U twice weekly was initiated for severe hypovitaminosis D (25-hydroxy vitamin D level <10 ng/mL).

Fish oil therapy was not offered due to concerns that in the setting of recurrent acute pancreatitis, dietary fat would increase chylomicron production and worsen the hypertriglyceridemia. Ezetimibe was not offered due to concerns of worsening hepatic function.

The patient was additionally noted to be hyponatremic with sodium levels as low as 127 mEq/L. Although calculations of serum osmolality were not obtained, we believe that this value was likely spuriously reduced secondary to the high presence of insoluble TG and LP-X in the plasma. Further contributions to hyponatremia stemming from the severe liver injury were additionally considered.

Because of presumed beta cell destruction by recurrent pancreatitis episodes, the patient developed diabetes mellitus. She was initiated on insulin therapy; however, the hemoglobin A_{1c} increased from 4.6% to 7.6%.

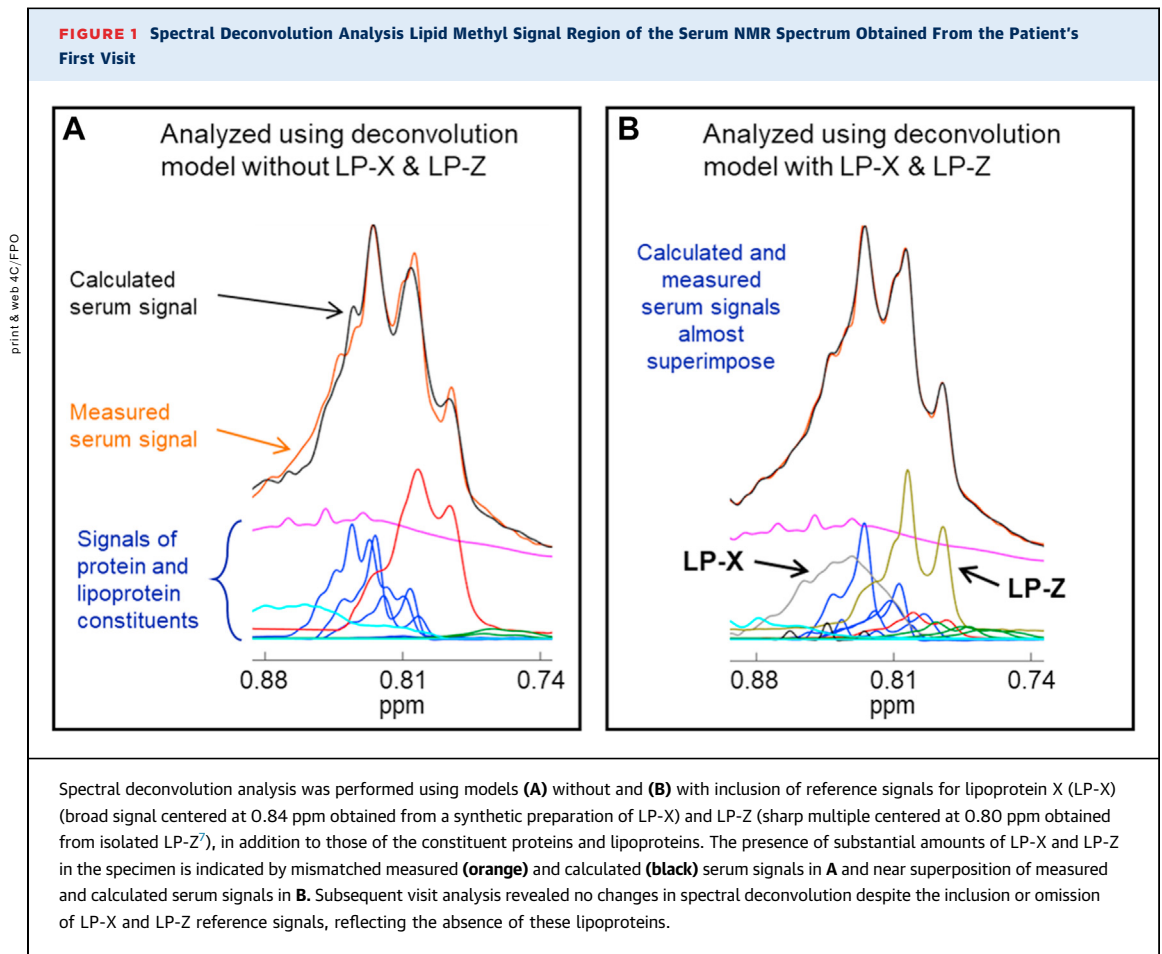
Finally, in light of persistent elevations in alkaline phosphatase, the gastroenterology service was consulted for management of liver hematoma and biliary stricture. Endoscopic retrograde cholangiopancreatography and biliary stenting were performed and serial imaging of the biliary hematoma was obtained. Subsequently, she developed an abscess at the site of the hematoma.

DISCUSSION

The initial case presentation suggested mixed (type 5) hyperlipoproteinemia, an uncommon disorder that results from impaired clearance of chylomicrons and very low-density lipoprotein particles.³ The condition is associated with new-onset or worsening hypertriglyceridemia that is aggravated by a secondary disorder such as diabetes mellitus. Treatment is

ABBREVIATIONS AND ACRONYMS

- HDL-C** = high-density cholesterol
- LDL-C** = low-density cholesterol
- LP-X** = lipoprotein-X
- LP-Z** = lipoprotein-Z
- NMR** = nuclear magnetic resonance
- RR** = reference range
- TG** = triglycerides
- WBV** = whole blood viscosity



aimed at TG reduction for the prevention of acute pancreatitis.³

Fenofibrate-statin therapy is often prescribed for TG reduction. Associations with severe liver injury are rare. The incidence of statin-induced acute liver failure is estimated at 2 in 1,000,000 and clinically significant fenofibrate-induced liver injury has an estimated incidence <0.3%.^{4,5} In this patient, fenofibrate-statin therapy resulted in severe cholestatic liver injury.

Cholestatic liver injury may be associated with elevations of the abnormal lipoproteins LP-X and LP-Z. LP-X arises when biliary phospholipids reflux into the plasma secondary to cholestasis. These phospholipids combine with non-esterified cholesterol and arrange in a multilamellar formation around an albumin core.^{2,6,7} LP-Z is an LDL-like particle characterized by high levels of TG in place of cholesterol esters.¹ The biochemical process responsible for its formation is unclear. In contrast to LP-X, which does not carry apolipoprotein-B, LP-Z contains apolipoprotein-B and is thus considered atherogenic.^{1,2,4,7}

As LP-X and LP-Z are found within the same density range as LDL, their presence can cause measured "LDL-C" to be both highly elevated and inaccurate.^{1,6} The patient's initial laboratory studies revealed a directly measured LDL-C of 662 mg/dL, a value incompatible with the 565 mg/dL total cholesterol level and 8 times higher than the 84 mg/dL value from 2 years prior. NMR-measured LDL particle number was extremely high (5,527 nmol/L) at the initial visit, 78% of which was accounted for by LP-Z (Table 1). A discordant, but elevated apolipoprotein-B level of 135 mg/dL was increased secondary to LP-Z.

High levels of LP-Z and LP-X can contribute to blood hyperviscosity. LP-Z particles are relatively small (18-20 nm) and homogeneously sized, which we hypothesize raises WBV secondary to particle concentration. LP-X particles are larger and heterogeneously sized (30-100 nm), which increases WBV due both to molecular size and increased propensity for aggregation.^{2,7,8} Hyperviscosity syndrome induced by LP-X has been previously described in a patient with primary biliary cholangitis, in whom elevations of LP-X were correlated with increased WBV and

TABLE 1 Lipid Panel, NMR Measures, Hepatic Panel With Model for End-Stage Liver Disease Score

Lab Value	Initial Pancreatitis Hospitalization June 2021	Referral Visit ^a September 2021	First Visit November 2021	Follow-Up Visit January 2022	7-Month Follow-Up June 2022
Total cholesterol, mg/dL	509	565	1,074	478	278
LDL-C, mg/dL ^b	–	662 (direct)	874 (NIH)	334 (NIH)	140 (NIH)
HDL-C, mg/dL ^b	24	16	9	103	126
TG, mg/dL	3,140	416	408	203	74
Apolipoprotein B, mg/dL	–	224	135	–	–
LDL particle number, nmol/L from NMR	–	–	5,527	3,906	–
LP-X, arbitrary units from NMR	–	–	2,407	192	–
LP-Z, nmol/L from NMR	–	–	4,328	1,532	–
Aspartate aminotransferase, U/L	13	108	537	212	74
Alanine aminotransferase, U/L	12	40	423	309	98
Alkaline phosphatase, U/L	84	708	1,249	1,004	624
Total bilirubin, mg/dL	0.8	16.8	10.7	2	0.6
Lipase, U/L	224	297	–	–	–
Albumin, g/dL	3.6	1.6	3.7	3.5	4.5
INR	1.1	1	1	1	1
Sodium, mEq/L	129	129	127	131	136
Creatinine, mg/dL	0.34	0.38	0.42	0.36	0.54
Hemoglobin A _{1c} , %	–	4.6	–	6.8	7.6
Model for End-stage Liver Disease score (points)	6	23	22	10	6

^aNIH calculation of LDL-C is obtained from the following formula: LDL-C = total cholesterol/0.948 - HDL-C/0.971 - (TG/8.56 + [TG × non-HDL-C]/2,140 - TG 2 /16,100) - 9.44). The use of the NIH method is limited in states where serum triglycerides exceed 800 mg/dL necessitating direct measurement of LDL-C from the sample. ^bHDL-C was directly measured. HDL-C = high-density lipoprotein cholesterol; INR = international normalized ratio; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LP-X = lipoprotein X; LP-Z = lipoprotein Z; NIH = National Institutes of Health; NMR = nuclear magnetic resonance; TG = triglyceride.

neurological symptoms.⁸ Correlations between LP-X and WBV remained consistent before and after plasma exchange for LP-X removal (R = 0.95, 95% CI: 0.84-0.99 and R = 0.95, 95% CI: 0.85-0.98, respectively). Neurologic symptoms improved with reduction of LP-X, LP-Z, and WBV.⁸ In our case, the presence of LP-X and LP-Z was associated with a high shear WBV of 5.5 cP (reference range [RR]: 3.7-4.4 cP), low shear WBV of 21.7cP (RR: 8.9-12.4 cP), and serum viscosity of 2.4 cP (RR: 1.4-1.8 cP) (Table 2).

Physiologically, increases in WBV cause sluggish microcirculatory blood flow, increased erythrocyte aggregation, and impaired perfusion.⁹ The symptoms of fatigue, blurred vision, paresthesia, and ataxia have recognized associations with hyperviscosity and

are described in other hyperviscosity syndromes such as hyper-immunoglobulin M syndrome or Waldenstrom’s macroglobulinemia.¹⁰

Treatment of LP-X and LP-Z dyslipidemia is based on alleviating the hepatic injury.¹ In patients with complications or debilitating neurological symptoms, plasmapheresis may be considered.^{2,8} In this case, hepatic recovery warranted a conservative approach.

FOLLOW-UP

At the 3-month follow-up exam, hepatic recovery was found to be associated with substantial reductions of LP-X and LP-Z levels (Table 1), normalization of serum viscosity to 1.7 cP (RR: 1.4-1.8 cP), high shear WBV to 3.8 cP (RR: 3.7-4.4 cP), low shear WBV to 12.5 cP (RR: 8.9-12.4 cP), and amelioration of neurological symptoms (Table 2). Body mass index remained unchanged at 31.7 kg/m².

At the 7-month follow-up exam, the patient remained asymptomatic, and reported increased energy. Body mass index remained elevated at 33 kg/m². Routine laboratory values showed significant improvements in total cholesterol (278 mg/dL), LDL-C (140 mg/dL), and TG (74 mg/dL). HDL-C was high at 126 mg/dL. Similarly, hepatic studies reflected improvement of intrinsic function (albumin, 4.5;

TABLE 2 Whole Blood and Serum Viscosity

Measured Blood Viscosity, cP	First Visit November 2021	Follow-Up Visit January 2022
Low shear RR (3.7-4.4)	5.5	3.8
High shear RR (8.9-12.4)	21.7	12.5
Serum viscosity RR (1.4-1.8)	2.4	1.7

RR = reference range.

INR, 1.0), reductions of aspartate aminotransferase (74 U/L), alanine aminotransferase (98 U/L), and alkaline phosphatase (624 U/L). Sodium levels normalized at 136 mEq/dL. The normalization of triglycerides is attributed to the resolution of LP-Z. We hypothesize that persistent elevations of alkaline phosphatase are likely secondary to obstructive etiologies such as biliary stricture, hematoma, and hepatic abscess that are unrelated to drug-induced liver injury. The elevated HDL-C was attributed to the impaired lecithin:cholesterol acyl transferase activity that accompanies obstructive liver disease. Worsening hemoglobin A_{1c} is attributed to suboptimal glucose control in the setting of pancreatitis-induced beta cell destruction.

CONCLUSIONS

LP-X and LP-Z dyslipidemia should be considered in the setting of severe hypercholesterolemia and cholestatic injury. Elevations of LP-X and LP-Z can

include the development of hyperviscosity syndrome, which can be highly disabling for the patient and lead to acute neurological events. Treatment is aimed at alleviating the hepatic injury.

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The blood viscosity measurements were provided by Rheovector, LLC. Mr Cho and Mr Kim are employees of Rheovector, LLC. Dr Otvos is an employee of LabCorp, Inc. Dr Rosenson has received research grants to his institution from Amgen, Arrowhead, Eli Lilly, and Regeneron; has received consulting fees from Amgen, Arrowhead, CRISPER Therapeutics, Eli Lilly, Precision BioSciences, Regeneron, and UltraGenix; has received nonpromotional speaking fees from Amgen, Kowa, and Regeneron; has received royalties from Wolters Kluwer (UpToDate); and has stock holdings in MediMergent, LLC. Dr Waksman has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Robert S. Rosenson, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1030, New York, New York 10029, USA. E-mail: robert.rosenson@mssm.edu. Twitter: [@DrRSRosenson](https://twitter.com/DrRSRosenson).

REFERENCES

1. Bedi S, Garcia E, Jeyarajah EJ, et al. Characterization of LP-Z lipoprotein particles and quantification in subjects with liver disease using a newly developed NMR-based assay. *J Clin Med*. 2020;9(9):2915.
2. Kattah L, Gómez A, Gutiérrez S, et al. Hypercholesterolemia due to lipoprotein X: case report and thematic review. *Clin Med Insights Endocrinol Diabetes*. 2019;12:1179551419-878687.
3. Greenberg BH, Blackwelder WC, Levy RI. Primary type V hyperlipoproteinemia. A descriptive study in 32 families. *Ann Intern Med*. 1977;87:526-534.
4. Tolman KG. Defining patient risks from expanded preventive therapies. *Am J Cardiol*. 2000;85:15e-19e.
5. Ahmad J, Odin JA, Hayashi PH, et al. Identification and characterization of fenofibrate-induced liver injury. *Dig Dis Sci*. 2017;62:3596-3604.
6. Ross A, Murphy GM, Wilkinson PA, Mills GL, Sherlock S. Occurrence of an abnormal lipoprotein in patients with liver disease. *Gut*. 1970;11:1035-1037.
7. Narayanan S. Lipoprotein-X. *CRC Crit Rev Clin Lab Sci*. 1979;11:31-51.
8. Rosenson RS, Baker AL, Chow MJ, Hay RV. Hyperviscosity syndrome in a hypercholesterolemic patient with primary biliary cirrhosis. *Gastroenterology*. 1990;98:1351-1357.
9. Nader E, Skinner S, Romana M, et al. Blood rheology: key parameters, impact on blood flow, role in sickle cell disease and effects of exercise. *Front Physiol*. 2019;10:1329.
10. Gertz MA. Acute hyperviscosity: syndromes and management. *Blood*. 2018;132:1379-1385.

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