Unusual Lipid and Metabolic Abnormalities Secondary to Alcohol Abuse

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Ingestion of large amounts of alcohol affects lipid metabolism. Secondary hyperlipidemia in patients who abuse alcohol usually is Fredrickson phenotype IV or, rarely, phenotype V (**Table 1**). Type IV hyperlipidemia is characterized by an accumulation of very-low-density lipoprotein (VLDL) on plasma electrophoresis. The accumulation of VLDL causes elevated triglycerides. Low-density lipoprotein (LDL) level usually is not altered. Very occasionally, these patients also have superimposed chylomicronemia (type V hyperlipidemia).[1–6] The mechanism of hyperlipidemia in the setting of alcohol abuse is complex and relates to fatty acid synthesis and clearance in the liver. This article reports a case of a patient with apolipoprotein (Apo) E polymorphism and alcohol abuse who had type IIb hyperlipidemia, characterized by elevated triglycerides and LDL. The patient also had features of Zieve syndrome (alcoholic liver disease, hemolysis, and severe hyperlipidemia in the setting of alcohol abuse).

CASE PRESENTATION
History and Physical Examination

A 41-year-old man presented to the emergency department with epigastric pain, nausea, vomiting, and fatigue of 4 days' duration. The patient had a 25 pack-year history of smoking, alcohol abuse (his last alcoholic drink was a few hours before presentation), and hyperlipidemia (elevated triglycerides and cholesterol). The patient did not have a history of diabetes mellitus, renal insufficiency, nephrotic syndrome, or obesity. There was no family history of premature coronary artery disease, hyperlipidemia, pancreatitis, xanthomas, or xanthelasmas. The patient was never treated for hyperlipidemia before this presentation but was counseled at multiple visits about smoking cessation and alcohol abstinence. The patient was not taking any medications.

The patient was 5 ft 8 in tall and weighed 132 lb. His blood pressure was 140/80 mm Hg, Heart rate was 90 bpm, and respiratory rate was 16 breaths/min. Physical examination revealed mild epigastric tenderness and tremors in the extremities; both resolved the next day, after being admitted to the medical floor and receiving intravenous fluids. Abdominal examination revealed no hepatomegaly or right upper quadrant tenderness; there was no splenomegaly or ascites. Fundus examination showed lipemia retinalis. No xanthomas or xanthelasmas were noted. The physical examination was otherwise normal.

Laboratory and Diagnostic Studies

Laboratory data on admission is shown in **Table 2**. Blood samples on admission were visibly lipemic and hemolyzed. The hemoglobin concentration had decreased from 15.7 g/dL (baseline) to 13.6 g/dL. A repeat fasting lipid profile 2 days later showed the following values: triglycerides, 818 mg/dL; total cholesterol, 882 mg/dL; high-density lipoprotein (HDL), 26 mg/dL (normal, 27–67 mg/dL); and LDL, 692 mg/dL (normal, 87–157 mg/dL). (The patient's fasting lipid profile during a period of alcohol abstinence 1 year before presentation was as follows: triglycerides, 77 mg/dL; total cholesterol, 222 mg/dL; HDL, 63 mg/dL; and LDL, 144 mg/dL.)

Serum lipoprotein electrophoresis on admission showed type IIb hyperlipoproteinemia. Apo E studies showed an epsilon 4/3 genotype. His lactate dehydrogenase level was 230 U/L. Amylase and lipase levels were within normal limits. Thyroid function was normal. Urinalysis was negative for proteinuria. Peripheral

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Table 1. Phenotypic Classification of Hyperlipidemia

Type	Lipid Profile	Clinical Disorder	Manifestations
I	↑ Chylomicrons, ↑ TG	Familial lipoprotein lipase deficiency, Apo CII deficiency	Asymptomatic; pancreatitis; hepatomegaly; splenomegaly
IIa	↑ LDL, ↑ cholesterol, ± ↑ TG	Familial hypercholesterolemia, familial defective Apo B100, polygenic hypercholesterolemia	Familial: xanthomas Polygenic: CAD
IIb	↑ LDL, ↑ VLDL ± ↑ TG, ↑ cholesterol	Combined hyperlipidemia	Asymptomatic; CAD
III	↑ VLDL, ↑ TG, ↑ chylomicrons	Dysbetalipoproteinemia	Asymptomatic; vascular disease; xanthomas
IV	↑ VLDL, ± ↑ TG, ↓ HDL	Familial hypertriglyceridemia	Asymptomatic; vascular disease
V	↑ Chylomicrons, ↑ VLDL, ↑ TG	Familial lipoprotein lipase deficiency, Apo CII deficiency	Same as type I

Apo = apolipoprotein; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; VLDL = very-low-density lipoprotein.

Table 2. Laboratory Values of Case Patient on Admission

Parameter	Value	Normal Range
Hemoglobin (g/dL)	13.6	13.5–18
Sodium (mEq/L)	116	136–143
Chloride (mEq/L)	80	98–107
Potassium (mEq/L)	8.9*	3.6–5
Blood alcohol (mg/dL)	286	—
Blood glucose (fasting, mg/dL)	92	65–110
Blood urea nitrogen (mg/dL)	11	7–21
Serum creatinine (mg/dL)	0.8	0.8–1.5
Aspartate aminotransferase (U/L)	317	15–46
Alanine aminotransferase (U/L)	378	7–56
Bilirubin (mg/dL)	4.9	0.2–1.3
Triglycerides (fasting, mg/dL)	8858	< 150
Cholesterol (fasting, mg/dL)	1155	< 200

*Highest value of 3 measurements.

smear showed no specific pattern; spherocytosis, microangiopathic phenomenon, and sickle cell anemia were ruled out. The patient's reticulocyte count was mildly elevated at 3% (normal, 1%–2%). Haptoglobin level was 30 mg/dL (normal, 16–200 mg/dL). Direct and indirect Coombs tests were negative. Phosphate level was 3.7 mg/dL (normal, 2.5–4.5 mg/dL).

Antinuclear antibody level was not measured, as the clinical suspicion of systemic lupus erythematosus was low. Computed tomography scan of the chest and abdomen was not performed, as the suspicion of lymphoma was low.

Treatment and Outcome

The patient was treated with volume expansion and vitamin supplementation. He was discharged and was advised to abstain from alcohol. Dramatic resolution of symptoms as well as laboratory abnormalities were noted 1 month later: total cholesterol, 220 mg/dL; triglycerides, 126 mg/dL; HDL, 65 mg/dL; LDL, 130 mg/dL; sodium, 135 mmol/L; chloride, 100 mmol/L; potassium, 4.6 mmol/L; aspartate aminotransferase, 24 U/L; alanine aminotransferase, 28 U/L; bilirubin, 0.7 mg/dL. Over the next year of follow-up, the patient had 1 hospital admission for similar symptoms. His laboratory values at that time were total cholesterol, 501 mg/dL; triglycerides, 289 mg/dL; HDL, 39 mg/dL; LDL, 204 mg/dL; aspartate aminotransferase, 295 U/L; alanine aminotransferase, 349 U/L; bilirubin, 3.3 mg/dL. He also had 1 clinic visit for a similar but less dramatic presentation when he began abusing alcohol again. His liver chemistries were normal during periods of abstinence, as noted by routine follow-up.

DISCUSSION
Hyperlipidemia Associated with Alcohol Abuse

There is a known association between excessive alcohol use and an increase in VLDL (type IV hyperlipidemia). There is also a less common association between alcohol use and type V hyperlipidemia, in which both chylomicrons and VLDL are increased. The increase in VLDL depends on the patient's weight, baseline lipid profile, amount of alcohol ingested, and genetic variation. Most studies have shown either no change or a slight decrease in levels of LDL when alcohol is used in excessive amounts.[1–5] This reduction in LDL is related to

lipoprotein lipase deficiency, which blocks the conversion of VLDL to LDL. In addition, alcohol consumption may contribute to alterations in lipoprotein metabolism involving cholesteryl ester transfer protein, phospholipid transfer protein, lecithin-cholesterol acyltransferase, hepatic lipase, paraoxonase-1, and phospholipases.[7]

In this case, we postulate that the paradoxical increase in LDL mainly is due to the effect of alcohol in the setting of his Apo E abnormality, as the patient's LDL returned to near normal levels after the alcohol consumption was stopped. This patient who abused alcohol had Apo E polymorphism with epsilon 4/3 genotype. Allelic variation in Apo E is known to have functional effects on lipid metabolism and LDL receptors.[8,9] Apo E4 has a higher affinity to the LDL receptor than the other Apo E isoforms. The enhanced lipid binding, via negative feedback, leads to down-regulation of LDL receptor synthesis and a secondary increase in LDL levels. Our patient probably had reduced clearance of LDL due to a decrease in uptake by the LDL receptor.[9] Smoking also can affect lipid metabolism.

Lussier-Cacan and colleagues[10] recently showed that alcohol consumption in women with epsilon 4/3 genotype can influence LDL and HDL levels. There is an increase in HDL levels when alcohol is used in moderation, but there may be a decline in HDL when alcohol is used in excessive quantities.[2,3,11–15] Notably, in the present case, the HDL value increased after the patient stopped consuming alcohol. In fact, there is evidence showing that a decrease in the level of HDL in a person who abuses alcohol can be used as a marker for hepatic damage.[16]

Hyponatremia Associated with Hyperlipidemia

Hyponatremia in the setting of hyperlipidemia is essentially an artifact (ie, pseudohyponatremia) when measured using flame emission spectrophotometry and when a diluted serum is used in the ion-selective electrode method (indirect-reading potentiometry). Measurement of sodium using the ion-selective electrode method with an undiluted serum specimen (direct-reading potentiometry) gives the true aqueous sodium content regardless of the serum lipid level. This method should be used when the specimen is visibly lipemic regardless of the sodium level, when there is a large discrepancy between measured and calculated plasma osmolality, and probably when there is severe hyperglycemia together with low sodium.[17,18] Life-threatening hypernatremia and other errors in management can occur when patients present with hyponatremia or even with normal sodium levels in these clinical situations.[19,20] An unusual cause for hyper-

kalemia (or pseudohyperkalemia) is severe hyperlipidemia, in which there is an increase in release of potassium from damaged erythrocytes.

Zieve Syndrome

This patient also had evidence of Zieve syndrome, the constellation of alcoholic liver disease, hemolysis, and severe hyperlipidemia in the setting of alcohol abuse.[21,22] In these patients, Zieve noticed transient jaundice, tremors in the extremities, and rapid improvement of symptoms with abstinence of alcohol.[21,22] Hemolysis in patients with Zieve syndrome is due to alcohol-induced vitamin E deficiency, which reduces polyunsaturated fatty acid levels and causes oxidation of reduced erythrocyte glutathione, leading to enzyme instability and erythrocyte hemolysis. Abnormalities in fatty acid oxidation cause changes in cell membrane composition, which leads to injury of both erythrocytes and hepatocytes. In some patients with Zieve syndrome, severe hypophosphatemia can cause reduced adenosine 5'-triphosphate levels, erythrocyte membrane rigidity, fragmentation, reduced erythrocyte surface area, and spheroidicity. Spherocytes are then trapped in the spleen.[23]

CONCLUSION

Type IIb hyperlipidemia (increased triglycerides and LDL) is unusual in patients with excessive alcohol ingestion; one usually sees only increased VLDL. Apo E polymorphism can cause elevated LDL in a patient with alcohol abuse. It is important to identify lipid abnormalities and to repeat lipid profiles in these patients. If resolution of the lipid abnormality is not accomplished by abstinence from alcohol, dietary changes and lipid-lowering agents should be employed to reduce the risk of premature coronary artery disease. Zieve syndrome is an interesting but often unnoticed association and can lead to hyperkalemia. Direct-reading potentiometry should be used to confirm sodium level in the setting of severe hyperlipidemia regardless of initial sodium level.   **HP**

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