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The work-up for mixed hyperlipidemia: A case study

This case demonstrates that a history, physical exam, and laboratory studies are all needed to determine if the disorder is primary, secondary, or both.

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A 42-year-old man with type 2 diabetes mellitus and hypertension was referred to our clinic for assessment of mixed hyperlipidemia found on routine investigation. Results of our physical examination were unremarkable. The patient had no xanthomatous deposits. His family history was strongly positive for type 2 diabetes. His medications included ramipril, glyburide, and hydrochlorothiazide.

In our further laboratory testing, a fasting blood sample revealed a grossly lipemic serum, with a total cholesterol level of 536.34 mg/dL (normal range=146.94-201.08 mg/dL), total triglyceride level of 5927.4 mg/dL (normal=31.15-151.3 mg/dL), and high-density cholesterol (HDL-C) level of 23.4 mg/dL (normal=35.1-93.6 mg/dL). His thyroid-stimulating hormone (TSH) level was 0.94 mIU/L (normal=0.49-4.67 mIU/L).

Results were in the normal range for urea, creatinine, electrolytes, bilirubin, alkaline phosphatase, alanine aminotransferase, and albumin. Hemoglobin A1c (HbA1c) was 9.5%.

Following clues to an accurate diagnosis

When the lipid phenotype is a mixed hyperlipidemia—a common disorder that becomes more prevalent with increasing age—investigate potential underlying disorders such as diabetes mellitus, renal failure, hypothyroidism, and chronic liver disease (**TABLE 1**). Ask about alcohol intake and use of medications including glucocorticoids and oral contraceptives. And explore the family history, particularly for premature heart disease, pancreatitis, and known lipid disorders. Epidemiologic studies have shown that higher-than-normal triglyceride levels increase the risk of coronary artery disease (CAD), and triglyceride levels greater than 500.44 mg/dL are associated with pancreatitis.[1]

What to look for in the physical examination. Measure body mass index (BMI), check blood pressure and carotid and peripheral pulses, and palpate the liver and thyroid. Inspect palms, soles, extensor surfaces of the arms, buttocks, and tendinous attachments for xanthomatous deposits.

Lab work. Order a fasting glucose test, renal panel, thyroid function tests, and a liver panel to detect or rule out diabetes, hypothyroidism, and renal and liver disease. Typically, in dyslipidemia due to excessive alcohol intake or estrogen use, HDL cholesterol is disproportionately elevated (**TABLE 1**). Patients with hypertriglyceridemia may also present with acute pancreatitis and relatively low amylase levels, due to interference by triglyceride-rich lipoproteins that can show falsely low amylase levels. Removal of chylomicrons from plasma by centrifugation before laboratory testing can eliminate such artifacts.[2] In addition, hypertriglyceridemia can interfere with biochemical measurement of glucose, leading to falsely normal levels in these patients.[3]

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TABLE 1

Secondary causes of hyperlipidemia

Underlying cause	Chylomicrons	VLDL	LDL	HDL	IDL	Lp(a)
Acromegaly		+				+
Acute intermittent porphyria			+			
Alcohol		+		+		
Anorexia nervosa			+			
Autoimmune disease	+				+	
Cushing's disease		+				
Diabetes mellitus (type 2)	+	+		–		
Glucocorticoids		+				
Hepatitis		+				
Hypothyroidism			+		+	+
Liver disease (severe)			–			
Monoclonal gammopathies					+	
Multiple myeloma					+	
Nephrotic syndrome			+			+
Obesity		+		–		
Oral contraceptives		+		+		
Renal failure		+				+

+, elevated; –, reduced.

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein a; VLDL, very low-density lipoprotein.

Adapted from: Rader DJ, Hobbs HH. *Harrison's Principles of Internal Medicine.* 2012.[10]

When the lipid phenotype is a mixed hyperlipidemia, investigate potential underlying disorders such as diabetes mellitus, renal failure, hypothyroidism, and chronic liver disease.

To further refine the diagnosis, order lipoprotein electrophoresis, which identifies mixed hyperlipidemias according to the Fredrickson classification (types I–V).[4]

Making sense of findings

Although patients with type 2 diabetes and hyperlipidemia most often have the type IV variety, they can also have other types, including type V. In uncontrolled diabetes, increased lipid metabolism mobilizes fat stores and increases VLDL and chylomicrons in plasma. Lipoprotein lipase activity is insulin dependent and is transiently reduced in insulin-deficient states, further increasing triglyceride levels.[5]

TABLE 2
Primary hyperlipidemia

Genetic disorder (Frederickson type)	Typical clinical findings
Familial lipoprotein lipase deficiency (type I)	Eruptive xanthomas, hepatosplenomegaly, pancreatitis
Familial apoprotein C-II deficiency (type I)	Eruptive xanthomas, hepatosplenomegaly, pancreatitis
Familial combined hyperlipidemia (type IIb)	Coronary or peripheral atherosclerosis
Familial dysbetalipoproteinemia (type III)	Palmar and tuberous xanthomas, coronary or peripheral atherosclerosis
Familial hypertriglyceridemia (type IV or V)	Eruptive xanthomas (type V)

Adapted from: Rader DJ, Hobbs HH. *Harrison's Principles of Internal Medicine*. 2012.[10]

Hypothyroidism is classically associated with elevated plasma LDL cholesterol, but is also sometimes linked with high plasma triglycerides. The elevated plasma LDL cholesterol in hypothyroidism is due to reduced expression of LDL receptors resulting in impaired clearance of LDL.[6] Elevated triglycerides in hypothyroidism are due to decreased lipoprotein lipase activity.[7]

Suspect primary (familial) hyperlipidemia (TABLE 2) if blood test results exclude such disorders as diabetes or hypothyroidism, and excessive alcohol intake and medication use have been ruled out. Some genetic causes of hyperchylomicronemia are rare and include familial lipoprotein lipase deficiency and apoprotein C-II deficiency. The differential diagnosis of mixed hyperlipidemia also includes familial combined hyperlipidemia (FCHL), familial dysbetalipoproteinemia, and familial hypertriglyceridemia.

FCHL can be difficult to differentiate from dyslipidemia of metabolic syndrome. A dominant inheritance pattern favors a diagnosis of FCHL, while environmental factors are more important in dyslipidemia of metabolic syndrome.[8]

How my patient's case resolved

My patient's case was consistent with secondary dyslipidemia due to diabetes and metabolic syndrome. But patients with triglyceride levels above 2001.77 mg/dL almost always have both a secondary and a genetic form of hyperlipidemia.[9] My colleagues and I suspected Fredrickson's type V hyperlipoproteinemia because of the high triglycerides. This was confirmed when the lipoprotein electrophoresis showed decreased alpha, increased prebeta, and normal beta fractions and chylomicronemia.

Treatment. Therapy choices differ depending on the type of mixed hyperlipidemia a patient has. However, fibrates are usually needed in addition to statins. (*Of note:* Statin-induced myopathy is more likely in patients who are also taking fibrates, so careful monitoring is important.)

I added fenofibrate, metformin, and rosuvastatin to the patient's regimen, which included ramipril, glyburide, and hydrochlorothiazide. I also recommended lifestyle modifications and arranged a consultation with a dietician.

Four weeks later, his fasting lipid profile had improved: Total serum cholesterol level was 213.45 mg/dL, triglyceride level was 825.5 mg/dL, and HDL-C level was 37.05 mg/dL. Apolipoprotein B100 was 2.54 g/L (normal=0.59-1.46 g/L). At follow-up 3 months later, the patient's total

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cholesterol level was 145.9 mg/dL, triglyceride level was 330.4 mg/dL, and HDL-C level was 27.84 mg/dL. JFP

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