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Clinical Case Study

A Woman with Pancreatitis and Hypertriglyceridemia

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CASE DESCRIPTION

A woman presented to the emergency department with abdominal pain, nausea, and vomiting. On examination, she had abdominal tenderness and a medical history of diabetes mellitus type 1, hypertension, end-stage renal disease, liver disease (hepatic steatosis), hypothyroidism, chronic obstructive pulmonary disease, and congestive heart failure. The patient denied alcohol use or abuse. Lipase was 680 U/L (reference interval, 13–60 U/L) and triglycerides were >4425 mg/dL [reference interval, <150 mg/dL (50 mmol/L)]. These results, along with clinical and radiologic findings, suggested a diagnosis of hypertriglyceridemia-mediated pancreatitis.

The patient was treated with insulin and heparin, but triglycerides remained >4425 mg/dL. Consequently, plasmapheresis was used to reduce the serum triglyceride concentrations on day 3 posthospital presentation, but triglycerides persisted at >4425 mg/dL (Table 1). The transfusion medicine team noticed the appearance of clear plasma during the next plasmapheresis course and called the laboratory to investigate.

Triglyceride testing in a reference laboratory followed (Table 1). The CDC method also revealed markedly increased triglycerides at 6620 mg/dL (74.8 mmol/L). However, triglycerides were 151 mg/dL (1.7 mmol/L) in a glycerol-corrected triglyceride assay (Roche Triglyceride/Glycerol Blanked Reagent, Roche Diagnostics). Glycerol concentrations were calculated (triglycerides, CDC − triglycerides, glycerol corrected) to be 6469 mg/dL (73.1 mmol/L) [reference interval, 3.5–32.7 mg/dL (0.04–0.37 mmol/L)]. In other words, 6469 mg/dL (73.1 mmol/L) of the 6620 mg/dL (74.8 mmol/L) in this sample represented free glycerol and not triglyceride-derived glycerol.

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QUESTIONS TO CONSIDER

1. What is measured in blanked and nonblanked triglyceride tests?
2. What conditions could lead to these findings?
3. How can the laboratory identify falsely increased triglycerides?

DISCUSSION

Most triglyceride tests used in clinical laboratories do not measure triglyceride itself but the glycerol hydrolyzed from the triglyceride by the action of lipase. This is followed by another sequence of enzymatic steps resulting in color formation and spectrophotometric measurement. In this method, any free glycerol in the sample contributes to the measured triglyceride amount. Increased free glycerol in a sample will falsely increase triglycerides unless a blanking method is used. In the glycerol blanking method, the difference of the noncorrected and glycerol-corrected triglyceride results represents the concentration of free glycerol. Although once a matter of debate, offering a glycerol-blanked triglyceride assay is not clinically necessary under most circumstances and would add unnecessary cost. Significant increases of free glycerol are uncommon in inpatient and outpatient populations *(1–3)*. Among laboratories enrolled in proficiency testing for triglycerides from the College of American Pathologists, only 7% report results using glycerol-blanked methods.

The laboratory results were suspicious for pseudohypertriglyceridemia. The workup of suspected pseudohypertriglyceridemia begins with measuring triglycerides after glycerol blanking, followed by identifying the source of hyperglycerolemia, whether endogenous or exogenous (Table 2). Glycerol kinase deficiency (GKD)[2] is the most commonly reported cause of increased glycerol concentrations in patients *(4)*. GKD is a rare X-linked recessive disorder affecting fewer than 200 000 individuals in the US. It can occur isolated with or without symptoms or combined, involving adrenal dysfunction or Duchenne muscular dystrophy *(5)*. The clinical presen-

[2] Nonstandard abbreviations: GKD, glycerol kinase deficiency; L, lipemic index(ices).

Table 1. Triglycerides and glycerol measurements.

Test	Reference interval	Results				
		Day 1	Day 2	Day 3	Day 5	Day 9
Triglycerides, mg/dL (mmol/L)	<150 (3.69)	>4425 (50)	>4425 (50)	>4425 (50)	3971 (44.87)	1315 (14.86)
Triglycerides, CDC method, mg/dL (mmol/L)	<150 (3.69)		6620 (74.8)			
Triglycerides, glycerol-corrected, mg/dL (mmol/L)	<150 (3.69)		151 (1.71)			
Glycerol, calculated, mg/dL (mmol/L)	3.5–32.7 (0.04–0.37)		6469 (73.1)			
		Before apheresis		After apheresis		

tation of GKD ranges from asymptomatic to critical metabolic crisis. GKD is identified in patients with chronic hypertriglyceridemia [usually <1000 mg/dL (11.3 mmol/L)] not responding to intensive exercise regimens, dietary modifications, and multiple triglyceride-lowering medications, with absence of metabolic syndrome signs, later found to have pseudohypertriglyceridemia *(4)*. The diagnosis of GKD is mostly a diagnosis of exclusion, and testing for glycerol kinase activity is not necessary for diagnosis *(5)*. Patients with GKD show varying degrees of glycerol kinase activity in leukocytes, and various mutations have been identified.

Intake of glycerol-containing products falsely increases triglyceride concentrations, which resolve after cessation. Glycerol is present in certain alcoholic beverages, medications, beauty products (e.g., lotions), cleaning products (e.g., soap and detergents), and parenteral nutrition *(4)*. Pseudohypertriglyceridemia is documented in individuals drinking glycerol as an alcohol replacement and for healthier skin, taking glycerin for glaucoma treatment, and undergoing oral glycerol test to evaluate for hearing loss *(6–8)*. Careful medical history and medication intake is necessary to identify exogeneous causes of hyperglycerolemia.

Table 2. Representative lists of potential causes of hyperglycerolemia.

Endogenous	Exogenous
GKD	Oral glycerol
Alcoholism	Certain alcoholic beverages
Hyperthyroidism	Glycerol-containing medications (e.g., propofol)
Severe hepatic disease	Detergents and beauty products

During our investigation, it was noted that all the samples from this patient had lipemic indices (L) <20. Although L is not considered a reliable indicator of triglyceride concentrations, L and the ratio between the logarithm of serum triglycerides and L are reported to be useful indicators of pseudohypertriglyceridemia in cases of exogenous glycerol intake and GKD, respectively *(7, 9)*. Therefore, we explored whether increased triglycerides and discrepantly low L could be used to investigate pseudohypertriglyceridemia in our laboratory. We reviewed triglyceride and L results from years 2012 to 2017 (n = 228 046). Linear regression statistics of results ranging from 150 to 4425 mg/dL (1.69–50 mmol/L) showed correlation between triglycerides and L ($R = 0.64$; $R^2 = 0.41$; $P < 0.0001$).

From our data, cutoffs were established to identify samples that should be visually evaluated. Pseudohypertriglyceridemia was suspected when:

- Triglycerides 500 to 1000 mg/dL (5.65–11.3 mmol/L) and L <10;
- Triglycerides 1001 to 2000 mg/dL (11.31–22.6 mmol/L) and L <20; and
- Triglycerides >2000 mg/dL and L <50.

However, operationalization of sample flagging using electronic alerts may not be feasible, thus preventing implementation of these rules. Initially, we implemented the above-mentioned steps for samples with triglycerides >4425 mg/dL and discrepantly low L (<50). These were retrieved for visual inspection and to repeat testing. Samples that did not appear lipemic were investigated for pseudohypertriglyceridemia. Other scenarios (e.g., repeat testing does not match original values) raised suspicion for other laboratory errors. Patients with GKD rarely have such high triglyceride concentrations. Moreover, the method used to derive these cutoffs lacked validation, and these institutional observations may not be adequate for universal use. Instead, laboratories should consider

similar approaches using their data and in the context of their operational capabilities and clinical needs. Communication between clinicians and the laboratory remains the best approach at the moment to investigate suspected spurious results (i.e., increased triglycerides in the absence of lipid disorders or unresponsive to therapy).

CONCLUSIONS

This patient declined family history of GKD or increased triglycerides. Given the history of liver disease, GKD was initially considered. Triglyceride concentrations in this patient were much higher than reported for GKD (usually <1000 mg/dL). Moreover, triglyceride concentrations decreased during her hospital stay without further intervention (Table 1), suggesting an exogenous glycerol source. The patient later reported a habit of soap ingestion. Another case of soap ingestion also presented with abdominal pain *(10)*, similar to her presentation. Glycerin in the soap was considered the most likely exogenous source of glycerol. The patient's triglyceride concentrations normalized over the following months.

Unless triglycerides are measured after glycerol-blanking, the presence of glycerol in a sample results in false triglycerides increase. Interference by high endogenous free glycerol should be considered in patients with high triglycerides not responding to treatment and in samples with discordant lipemia (e.g., no visible or measured turbidity) for the degree of triglyceride concentrations. Identification of pseudohypertriglyceridemia is essential for adequate diagnosis and treatment of patients with increased glycerol.

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A. Farooq, provision of study material or patients.

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POINTS TO REMEMBER

- Hyperglycerolemia can be observed in disorders of glycerol metabolism, alcoholism, post-heparin therapy, and in severe liver disease, or it can be caused by exogenous intake of glycerol present in glycerol-containing medications, certain alcoholic beverages, detergents, and beauty products.
- GKD is the most commonly reported cause of increased glycerol concentrations in patients.
- Free glycerol interferes with commonly used triglyceride assays causing pseudohypertriglyceridemia.
- Glycerol-blanked triglyceride assays should be used to determine the concentration of triglycerides and free glycerol in cases of pseudohypertriglyceridemia.
- Pseudohypertriglyceridemia should be considered in patients with hypertriglyceridemia not responding to treatment and in patients presenting signs of unstable metabolic disorders.
- Discrepantly high triglycerides and very low lipemic indices may be indicative of pseudohypertriglyceridemia.

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