Glycerol Kinase Deficiency with Increased Triglycerides and Weight Gain: Pseudo or Real?

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CASE DESCRIPTION

A 20-year-old male was found to have increased triglycerides (TG) (777 mg/dL [8.78 mmol/L], reference interval: <150 mg/dL [<1.7 mmol/L]), with normal total cholesterol (159 mg/dL [4.1 mmol/L], reference interval: <200 mg/dL [<5.2 mmol/L]) and normal glucose (80 mg/dL [4.4 mmol/L], reference interval: 65–99 mg/dL [3.6–5.5 mmol/L]) concentrations. The patient was diagnosed with glycerol kinase deficiency (GKD) and adrenal hypoplasia congenita (AHC) at two-and-a-half years of age during an admission for severe hypoglycemia. He has a contiguous Xp21 microdeletion (Xp21.3-p21.2), a 256 Mb deletion resulting in AHC (due to a nuclear receptor subfamily 0 group B member 1 [*NR0B1*] gene deletion), GKD (due to a glycerol kinase [*GK*] gene deletion), and a small 3' terminal deletion of the dystrophin gene (*DMD*), the latter of unknown clinical significance. He was followed by pediatric endocrinology and received treatment with daily fludrocortisone (0.1 mg in the morning and 0.05 mg at night) and hydrocortisone (5 mg, 3 times a day), and weekly testosterone (26 mg). He had an 8.5 kg weight gain over the previous year, resulting in a current body mass index (BMI) of 32.2 kg/m2 (approximately 97th percentile; in Class 1 [low-risk] obesity range). A lipid panel was ordered and repeated, which demonstrated markedly increased TG concentrations on both occasions, and decreased high density lipoprotein (HDL) cholesterol on the repeated test (35 mg/dL [0.9 mmol/L], reference interval: >40 mg/dL [>1.0 mmol/L]) (Table 1).

Visual inspection of the specimen showed clear plasma with slight turbidity (Fig. 1A). The lipemia index (L-index) of the specimen, measured by bichromatic turbidimetry, was 30 (Roche Cobas), which was considered inappropriately low and inconsistent with such a markedly increased TG concentration. Suspecting pseudohypertriglyceridemia due to glycerol interference with the TG assay, the glycerol concentration was measured directly by enzymatic assay (Randox Laboratories), and showed increased glycerol at 736.5 µmol/L (reference interval: 28 to 108 µmol/L). Despite being clearly increased, the concentration of measured glycerol did not fully account for the measured TG. Furthermore, the calculated TG/L-index ratio (log-transformed TG concentration divided by the log-transformed L-index, 0.66) was lower than that previously reported in patients with GKD (0.80) (1).

Due to the presence of GKD and 2 features of metabolic syndrome in this patient (increased BMI, decreased HDL cholesterol), additional specimens were collected for lipoprotein metabolism profile assessment, which included ultracentrifugation, selective precipitation, electrophoresis, and direct measurement of cholesterol and TG in isolated lipoprotein fractions. Cholesterol was measured by a cholesterol ester hydrolase–cholesterol oxidase–peroxidase chromogenic method.TG was measured by hydrolysis to glycerol, followed by phosphorylation (by glycerol kinase) and oxidation (by glycerol phosphate oxidase) to dihydroxyacetone phosphate and hydrogen peroxide; hydrogen peroxide then reacted with 4-aminophenazone and 4-chlorophenol in the presence of peroxidase in a Trinder end point

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reaction to form 4-(p-benzoquinonemonoimino)-phenazone, which was measured spectrophotometrically at wavelengths (primary/secondary) 700/505 nm.

Figure 1 shows that in addition to hyperglycerolemia, true hypertriglyceridemia was also present. Distinct bands for chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and HDL were noted on electrophoresis. Increased VLDL-TG, LDL-TG, and chylomicron-TG indicated the presence of true hypertriglyceridemia components, most consistent with hyperlipoproteinemia type IV (increased VLDL together with a minor chylomicron band in otherwise clear specimens could be due to insufficient fasting or slow clearance of a fatty meal; however, all specimens collected from our patient were fasting, per provider) or type V (increased VLDL and chylomicrons). As shown in Table 1, and in agreement with previous findings, the total cholesterol concentration was within the reference interval, while the HDL cholesterol concentration was decreased. Although there was an increased HDL-TG concentration at 539 mg/dL (6.09 mmol/L), we did not observe a strong HDL electrophoresis band. Since the TG measurement in the HDL fraction was also based on measurement of glyceride after ultracentrifugation (to isolate the HDL component), the increased HDL-TG in the absence of strong HDL electrophoresis bands was consistent with hyperglycerolemia.

QUESTIONS TO CONSIDER
1. How is TG measured in serum?
2. What are common causes of pseudohypertriglyceridemia?
3. How can TG concentration be determined without the interference from endogenous glycerol?

Table 1. Patient laboratory results.

	Baseline	Day 10	Day 26	Day 65
Cholesterol, total, mg/dL (reference interval: <200)	159	159		
High-density lipoprotein (HDL) cholesterol, mg/dL (reference interval: ≥40)	41	**35**		
Triglycerides (TG), mg/dL (reference interval:<150)	**777**	**833**		**993**
Glycerol, μmol/L (reference interval: males 28 to 108; females 36 to 120)			**736.5**	
Lipoprotein metabolism profile				
Total cholesterol, mg/dL (reference interval:<200)				149
Low-density lipoprotein (LDL) cholesterol, mg/dL (reference interval: <100)				91
LDL-TG, mg/dL (reference interval: ≤50 mg/dL)				**61**
High-density lipoprotein (HDL) cholesterol, mg/dL (reference interval: males ≥40 mg/dL, females ≥50 mg/dL)				**28**
HDL-TG, mg/dL (reference interval <30)				**539**
Apolipoprotein B, mg/dL (reference interval: <90)				72
Very low-density lipoprotein (VLDL) cholesterol, mg/dL (reference interval: <30)				25
VLDL-TG, mg/dL (reference interval: <120)				**291**
Chylomicron cholesterol, mg/dL (reference interval: undetectable)				5
Chylomicron-TG, mg/dL (reference interval: undetectable)				**102**

Bolded values highlight results outside of the reference intervals.

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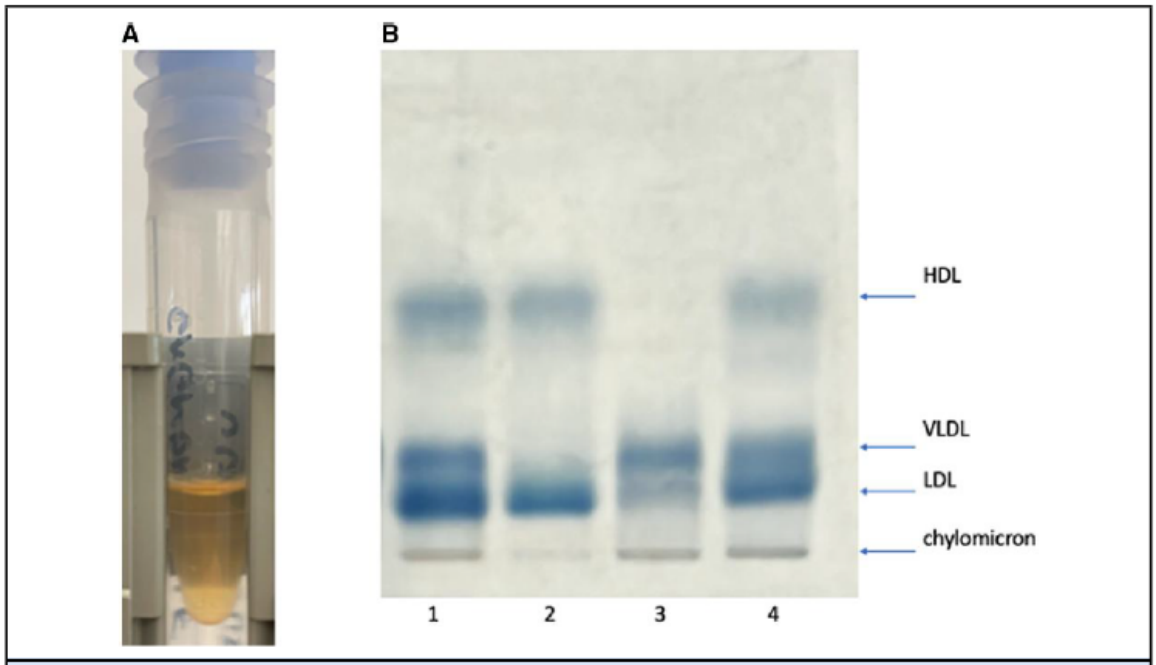

Fig. 1. Patient plasma sample and lipoprotein metabolism profile. (A), Plasma sample visualization; (B), lipoprotein metabolism profile (patient Lanes 1 to 3, control Lane 4). Lane 1: whole plasma; Lane 2: plasma d > 1.006 fraction (LDL, HDL); Lane 3: plasma d < 1.006 fraction (chylomicron, VLDL); Lane 4: control. Cholesterol mmol/L = mg/dL × 0.02586; triglycerides mmol/L = md/dL × 0.01129.

REFERENCE

1. De Haene H, Taes Y, Christophe A, Delanghe J. Comparison of triglyceride concentration with lipemic index in disorders of triglyceride and glycerol metabolism. Clin Chem Lab Med 2006;44:220–2.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the May 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/5 and follow the link to the Clinical Case Study and Commentaries.

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